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UNITED STATES DISTRICT COURT

FOR THE SOUTHERN DISTRICT OF CALIFORNIA

BECKMAN COULTER INC. and ORCHID CELLMARK INC., Plaintiffs, v. SEQUENOM, INC., Defendant.	Case No. 08 CV 1013 MMA POR **DECLARATION OF DR. LARRY J. KRICKA IN SUPPORT OF PLAINTIFFS' OPENING CLAIM CONSTRUCTION BRIEF** Date: June 11, 2009 Time: 1:30 p.m. Location: Courtroom 5 Judge: Honorable Michael M. Anello
AND RELATED COUNTERCLAIM	

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I, Dr. Larry J. Kricka, declare as follows:

I. PERSONAL AND PROFESSIONAL BACKGROUND

1. I have been retained as an expert by Plaintiffs Beckman Coulter Inc. and Orchid Cellmark Inc. ("Plaintiffs"). I have personal knowledge of the matters stated herein and if called to testify as a witness, I could and would competently testify thereto.

2. I received my Bachelor of Arts and a D.Phil. in Chemistry from York University, England in 1968 and 1971, respectively. I have served as a Professor in the Department of Pathology and Laboratory Medicine at the University of Pennsylvania and as the Director of the General Chemistry Laboratory at the Hospital of the University of Pennsylvania since 1987. I have received numerous awards in my field of study including: the American Association for Clinical Chemistry Ullman Award (2006) and the Award for Outstanding Contributions to Clinical Chemistry in a Selected Area of Research (1998), the Rank Prize for Opto-Electronics (1991), the Queens Award for Technological Achievement (1990), the Prince of Wales Award for Innovation and Production (1989), the Department of Trade and Industry's Industry Year Award for Technology Transfer (1986), and the Society of Analytical Chemistry Silver Medal (Royal Society of Chemistry, UK). I am a Fellow of the Royal College of Pathologists, the Royal Society of Chemistry, and the National Academy of Clinical Biochemistry. I currently hold and have held offices in national and international organizations including the International Federation of Clinical Chemistry, the Clinical and Laboratory Standards Institute and currently serve on the Program Coordinating Committee of the American Association for Clinical Chemistry. In 2001, I served as President of the American Association for Clinical Chemistry. I currently hold and have held editorial posts for a number of scientific publications. I am the Editor-in-Chief of the Journal of Bioluminescence and Chemiluminescence. I serve on the Editorial Boards of Clinical Chemistry, Analytical Biochemistry, Lab-on-a-Chip, and the Journal of Medical Sciences. I currently serve as a reviewer for various scientific journals. I have more than 20 years of experience in the field of nucleic acid labeling and detection. I am and have been a Principal Investigator on a number of research grants concerning immunoassays, DNA-based diagnosis, and enhanced luminescence associated with nucleic acid labeling. I have extensive experience in ligand binding assays, clinical

diagnostics, microanalytical techniques, nanotechnology and luminescent detection techniques. I have also authored or co-authored over 500 publications and serve on numerous editorial boards and scientific advisory committees. My professional background is in clinical chemistry and laboratory medicine. Among other things, my research since 1973 has explored and developed luminescence-based enzyme and ligand-binder assays, tests for alcohol abuse, high-resolution analytical methods for clinical analysis, immunoassay interferences, and applications for analytical and preparative microchips. Current research in my laboratory continues to focus on analytical applications of microchips for genetic testing, immunoassay interferences, and applications of nanotechnology in nucleic acid testing. My curriculum vitae provides further details on my qualifications, and a list of my publications, is appended as to this declaration.

II. TASK

3. I was asked review the following U.S. Patents: U.S. Patent Nos. 5,888,819 (the "'819 patent"), 6,004,744 (the "'744 patent"), and 6,537,748 B1 (the "'748 patent") (collectively, the "patents-in-suit"). I was asked to provide expert opinion testimony that would assist the Court in determining the meaning of claim terms of the patents-in-suit.

III. MATERIALS CONSIDERED

4. My opinions are based on my educational background, industry knowledge, research in the relevant technology of the patents, and understanding of basic science principles and practices. As part of my analysis of the patents-in-suit and forming the bases of the opinions in this report I have considered the patents-in-suit, their prosecution histories, the references cited in the patents-in-suit, and proceedings of the two interferences. At times, I also reviewed extrinsic evidence cited by the parties, including relevant section of dictionaries and scientific journal to confirm the ordinary meaning of some of the terms.

5. I also reviewed the Joint Claim Construction Charts, Joint Claim Worksheets And Joint Hearing Statement ("the Joint Statement") that were filed on February 20, 2009. In Exhibit B of the Joint Statement, both parties present their proposed definitions for the claim terms, as well as the intrinsic and extrinsic evidence that the parties rely on in support of their respective definition. I also used this document to consider and analyze the proposed claim constructions of the parties.

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IV. CLAIM MEANING

6. I understand that the words of a patent claim are generally given their ordinary and customary meaning from the perspective of one of ordinary skill in the relevant art.

7. Based on my experience and knowledge of the field of the patents-in-suit, I find that one of ordinary skill in the art at the time of the invention would have had a general working knowledge of the structure and reactions of nucleic acids, and would also understand the general principles of nucleic acid hybridization and the various assays based on this principle. Additionally, one of ordinary skill in the art would understand the technology of nucleic acid immobilization, nucleic acid labeling and polymerase reactions. Thus in my opinion, one of ordinary skill in the art at the time of the invention would be a person having an MD, PhD, or similar degree in the chemical or biological sciences, or the experiential equivalent thereof, as well as at least some amount of laboratory experience. I consider myself to be one of at least ordinary skill in the art.

8. I have reviewed Exhibit B of the Joint Statement, which sets forth the terms for which the parties have not agreed on construction. I have analyzed each party's interpretation and support for the meanings of these disputed terms. I disagree with the proposed claim constructions offered by Sequenom, Inc. ("Defendant"). Based upon my analysis and my understanding of how the terms would be interpreted by one of ordinary skill in the art at the time of the invention, I have determined that the claim constructions set forth by Plaintiffs are the correct interpretations.

V. THE PATENTS-IN-SUIT

9. The '819 patent was issued on March 30, 1999. The '744 patent, the next patent in the series, was issued on December 21, 1999. The specification of this patent contains some differences from the '819 specification, including an additional example, four additional figures, and some modifications to the Embodiments section. The final patent in the series, the '748 patent, was issued on March 25, 2003 and its specification is similar to the specification of the '744 patent. For simplicity, I will cite to the specification of the '819 whenever I refer to text common to the specifications of the three patents-in-suit.

10. The three patents-in-suit relate to methods and reagent compositions for detecting and identifying a particular type of variation in the genetic code of organisms called a "single

nucleotide polymorphism ("SNP") using single base extension technology ("SBE"). This is known in the industry as SNP genotyping. Generally, a SNP is a DNA sequence variation that occurs when a single nucleotide, A,T, C or G, in the genome sequence is altered.

VI. BACKGROUND OF THE RELEVANT TECHNOLOGY

A. Structure Of Genetic Material

11. Nucleic acids, such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), are organic chemical compounds that carry the genetic information necessary for life. Nucleic acids are polymers: thread-like molecules (strands) composed of repeating, but not necessarily identical, chemical subunits. The subunits in nucleic acids are called nucleotides. Therefore, nucleic acids like DNA or RNA are often called polynucleotides because they contain many (poly-) nucleotides. Shorter nucleic acids (from 2 to ~30 nucleotides) are sometimes called oligonucleotides – meaning a few (oligo-) nucleotides.

12. As seen in Figure 1 below, each nucleotide in a nucleic acid is composed of three distinct building blocks: a nitrogenous base, a pentose sugar ring, and a phosphate group (Figure 1 A). A nitrogenous base is a molecule that contains nitrogen and has basic, as opposed to acidic, properties. A pentose sugar is a type of sugar molecule containing five (pent-) carbon atoms. Phosphate is the term for a phosphorous atom surrounded by four oxygen atoms.

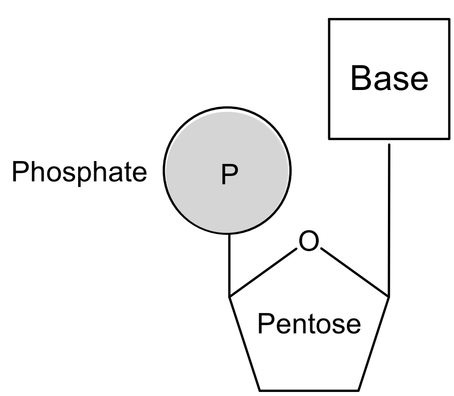


Figure 1A. Nucleotide structures. A. The three basic building blocks of a nucleotide - the base, the pentose sugar ring and the phosphate.

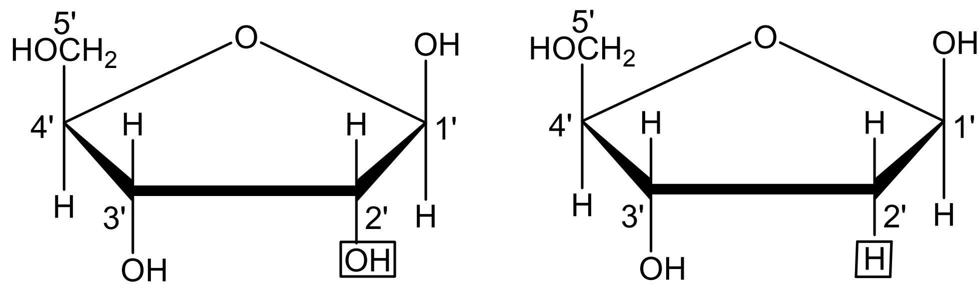


Figure 1B. Structures of ribose (the pentose sugar in RNA) and deoxyribose (the pentose sugar in DNA).

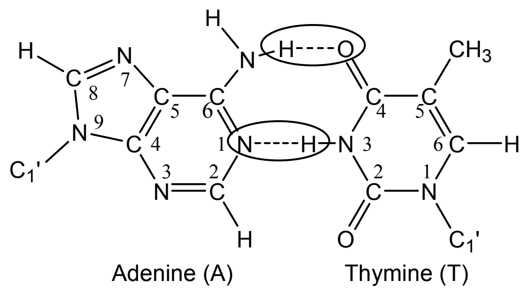
13. Figure 1B also shows the standardized system for numbering the positions of the carbon atoms in the pentose sugar ring. The carbons in the pentose are denoted: 1', 2', 3', 4', and 5' (which read "one prime," "two prime," etc.). The numbering begins on the carbon covalently bonded to the base (1') and continues clockwise around the ring (2' through 5'). The 1' position is where the nitrogenous bases covalently bind to the ring. The 2' position is the only place where RNA differs from DNA: RNA has both a hydroxyl group (-OH) and a hydrogen atom (-H) at the 2' position, whereas DNA has two hydrogen atoms at the 2' position). The 3' position is where the phosphate group of another nucleotide will covalently bind when creating a polynucleotide chain. The 5' position is covalently bound to at least one phosphate group. It is the hydroxyl groups at the 2'- and 3'-positions that are absent in dideoxynucleotides.

14. When the various nucleotide units link together to form polynucleotides, the phosphate groups form covalent linkages between the nucleotides, called phosphodiester bonds. These phosphodiester bonds link the 5' position of one nucleotide's pentose sugar to the 3' position of another nucleotide's pentose sugar. The chain of pentose sugars linked together through phosphodiester bonds is called a sugar-phosphate backbone, and it provides structural support for the different nitrogenous bases.

15. In DNA and RNA, the sequence of nitrogenous bases covalently bonded to the sugar-phosphate backbone encodes genetic information. In DNA, there are four common types of bases as shown in Figure 2: adenine ("A"), cytosine ("C"), guanine ("G"), and thymine ("T"). In RNA, a base called uracil ("U") replaces T, but three of the bases – A, C, and G – are the same as those in DNA. Each of the five common types of nitrogenous bases can be classified either as a

pyrimidine (T, C, and U) or a purine (A and G).

Adenine-Thymine base pair



Guanine-Cytosine base pair

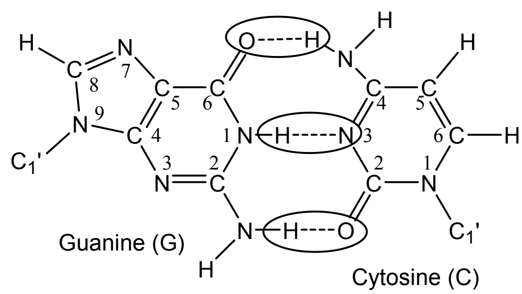


Figure 2. The bases in DNA and RNA - adenine ("A"), cytosine ("C"), guanine ("G"), and thymine ("T"). In RNA, a base called uracil ("U") replaces T

B. Hybridization Properties of Nucleic Acids

16. Hybridization is an important property of nucleic acids and is the basis of the binding of single stranded DNA molecules to produce the familiar double helix form of DNA (Figure 3A). This type of binding is exploited in DNA assays because under proper conditions, hybridization can be a reliable and highly specific technique. Hybridization is the binding of two separate, complementary strands of nucleic acids to form a nucleic acid hybrid – a stable complex of the two strands (sometimes called a duplex).

17. Two complementary nucleic acid strands hybridize through base pairing that is brought about by hydrogen bonding between chemical groups on the bases (Figure 2). Each type of base is only complementary to one other type of base. For example, the nucleotide A only pairs with T in DNA (or U in RNA), while C only pairs with G. This exclusive pairing is shown in Figure 3B where the nucleotide sequence 5'-A-G-G-T-A-C-3' hybridize to the complimentary

oligonucleotide with the sequence 3'-T-C-C-A-T-G-5'.

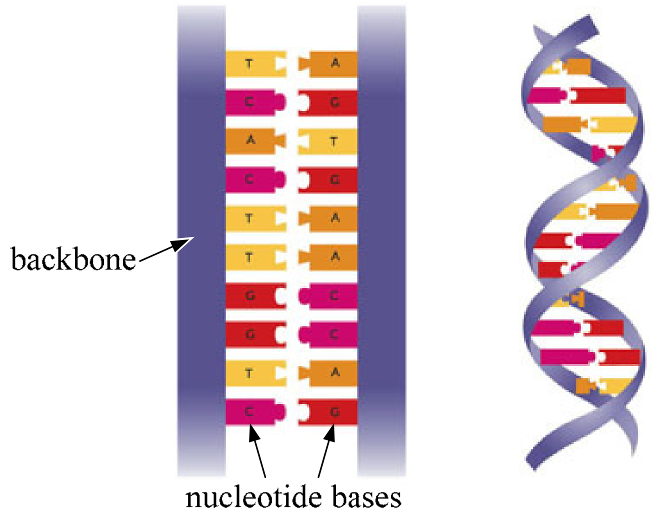


Figure 3A. Base pairing. A. The double helix form of DNA in which the two complementary strands are held together by the nucleotide base pairing interaction.

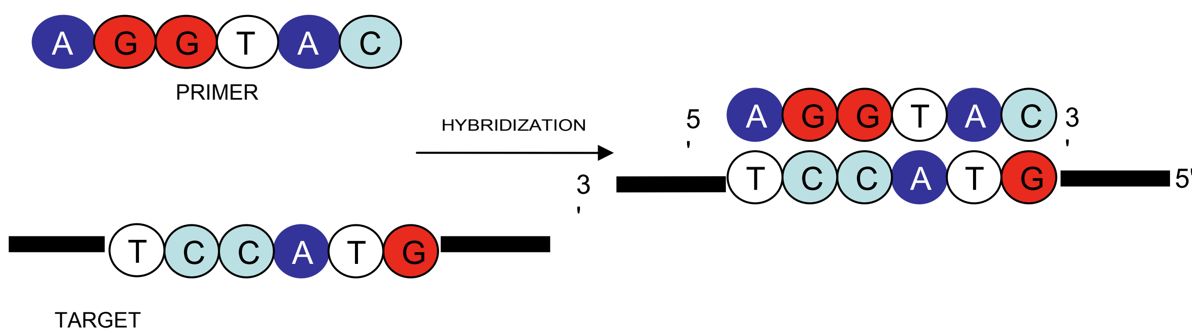


Figure 3B. Base pairing between adenine and thymine, and between guanine and cytosine, that underlies nucleic acid hybridization.

18. The ability of two complementary nucleic acid strands to hybridize can be used as the basis of a variety of tests. For instance, in SBE assays, a nucleic acid with a known sequence of nucleotides, is called a "primer". The primer will find and hybridize with a complementary sequence of nucleotides in a target nucleic acid. This target nucleic acid, often called a "target" or “template,” is usually a nucleic acid in a biological sample that a scientist wishes to detect the existence of, determine the sequence of, or measure the amount of, in the sample. The primer will

bind strongly and preferentially to complementary sequences in the target under hybridizable conditions creating a hybrid. After separating unhybridized primers or targets from the hybrids by washing, the hybrids direct a DNA polymerase to initiate attachment of a nucleotide at the 3' end of the hybridized primer. This polymerase-catalyzed attachment event can be detected through use of a label covalently bonded to or incorporated into the nucleotide. As explained in more detail below in Section IV.E, a label (sometimes called a tag or marker or tracer) is anything that functions as a means of identification (American Heritage Dictionary of the English language, Morris W, editor, Houghton Mifflin Co., Boston. 1980, p. 730) and it can have properties that make it either directly or indirectly detectable.

C. Extension of Nucleic Acid Molecules

19. Extension of nucleic acid molecules is a process by which a nucleic acid primer that has been hybridized to a single stranded nucleic acid molecule is grown or extended when a nucleic acid polymerase adds additional nucleotides to the 3' end of the primer.

20. A polymerase is an enzyme (e.g., DNA polymerase, RNA polymerase) that catalyzes the formation of polynucleotides of DNA or RNA from deoxyribonucleotides. This is also called extension. Two examples of polymerases that incorporate nucleotides or nucleotide analogs are Sequenase and Taq. (‘819 patent, col. 14, lines 58-62, col. 16, line 53). As a group, nucleotides used to extend a nucleic acid strand are typically called deoxynucleotide triphosphates (“dNTPs”). The common dNTPs are: dATP, dCTP, dTTP, and dGTP. A dNTP has a hydroxyl group at the 3' position of the pentose sugar that will bond to another nucleotide to extend the strand. The extension reaction occurs in only one direction by adding dNTPs to the 3' end of the primer because that is the end of the primer that has the hydroxyl group (the “OH”) at the 3' position which is necessary for the extension reaction to occur. Using base pairing interactions, a polymerase takes dNTPs from solution, and catalyses the synthesis of a nucleic acid molecule.

21. In single base extension reactions, two important properties of a polymerase are that it will utilize terminators as substrates, and it is primer-template dependent. Single base extension reactions utilize a polymerase to extend the 3' end of a primer hybridized to a nucleic acid template by a single base.

D. Terminators

22. The term "terminator" (or chain terminator) is used for a compound that will terminate the polymerase–catalyzed extension of the 3' end of one strand in a double-stranded (ds) nucleic acid molecule.

23. Termination can be achieved through a number of mechanisms. Removal of the 3'-hydroxyl group from the sugar ring eliminates the point of covalent binding for subsequent nucleotides, and this is the mechanism of termination in the best-known terminators, the dideoxynucleotide triphosphates (the "ddNTPs") (see Figure 4 below). These nucleotide analogs differ from the natural nucleotides – the hydroxyl groups on the pentose sugar ring at the 3'-positions are replaced by hydrogen atoms. In the normal polymerase-catalyzed sequential addition of dNTPs on the 3' end of a nucleic acid molecule, a covalent bond is formed between the 3'-hydroxyl of the terminal nucleotide and the 5'-triphosphate of the dNTP being added to the end of the molecule. If a ddNTP is added, then it becomes the terminal nucleotide. As the newly incorporated ddNTP lacks a 3'-hydroxyl group, formation of a covalent bond with the 5-triphosphate of the next dNTP is not possible, and the chain extension reaction is "terminated," hence the naming of such compounds such as ddNTPs as "chain terminators" or "terminators" (King RC, Stansfield WD. A dictionary of genetics. Oxford University Press, 5th edn, 1997, pps. 57 and 98).

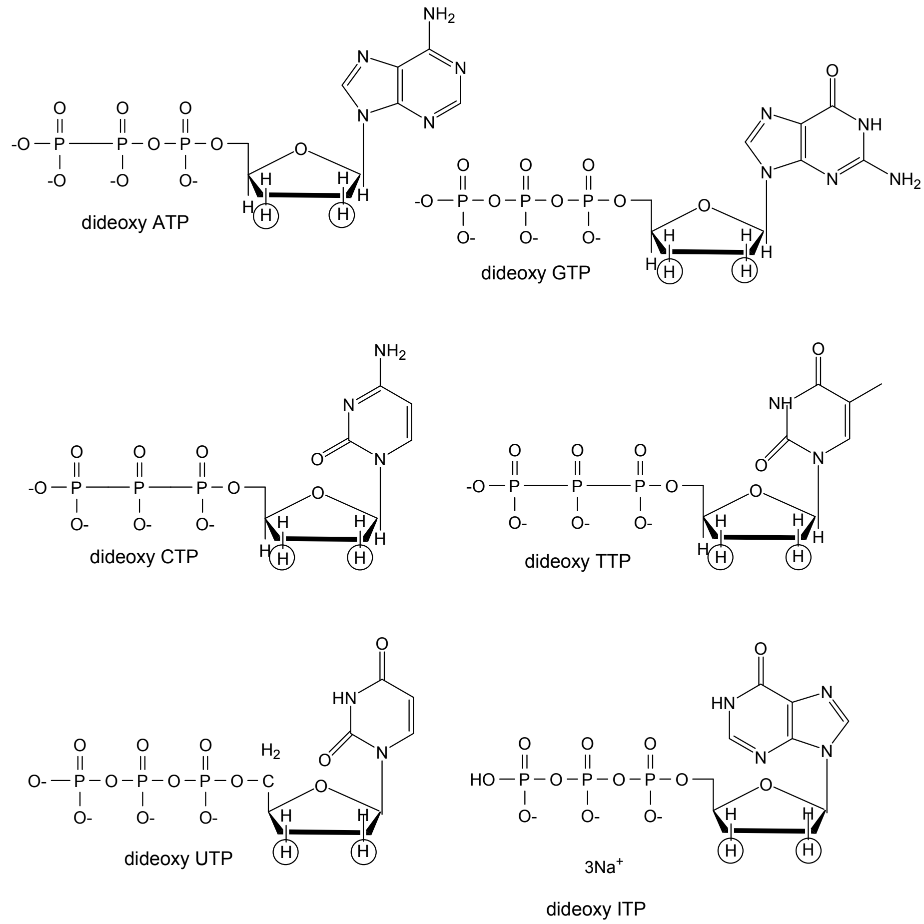


Figure 4. Structures of ddNTP terminators, dideoxyATP (ddATP), dideoxyGTP (ddGTP), dideoxyCTP (ddCTP), and dideoxyTTP (ddTTP), dideoxyUTP (ddUTP), and dideoxyITP (ddITP).

24. A nucleotide analog can function as a terminator even if the 3'-hydroxyl group is present on the sugar ring. In the case of arabinoside triphosphate ('819 patent, col. 5, lines 14-15; col. 8, lines 45-46), the 2'-hydroxyl group is in a trans-orientation to the 3'-hydroxyl group and this stereochemical arrangement renders it inactive with the polymerase (Mikita T, Beardsley GP. Functional consequences of the arabinosylcytosine structural lesion in DNA. Biochemistry 1988;27:4698-4705).

25. Generally, an analog (or analogue) is a compound whose structure is related to that of another compound but whose chemical and biological properties may be different. A nucleotide analog is thus a compound whose structure is related to that of a nucleotide but whose chemical and biological properties may be different. The scope of structural modifications in a nucleotide analog includes modification in the base, sugar or triphosphate portions of the nucleotide (Saenger W. Principles of nucleic acid structure. New York: Springer, 1984, p 159-200).

26. For example, 2',3'-dideoxynucleoside triphosphates are analogs of the normal 2'-deoxynucleoside triphosphates (King RC, Stansfield WD. A dictionary of genetics. Oxford:Oxford University Press, 5th edn, 1997, pp. 57 and 98).

27. The patents identify two types of analogs – nucleotide analogs ('819 patent, col.5, line 14) and non-natural nucleotide analogs ('819 patent, claim 30). The nucleotide analogs are analogs of the natural nucleotides (e.g., dATP), and non-natural nucleotide analogs are nucleotides that do not normally occur in nature, as exemplified by 7-deaza-2'-deoxyguanosine ('819 patent, claim 31).

28. The '819 patent claims "terminator nucleotide analogs," thus a terminator nucleotide analog is a nucleotide analog that is a terminator of a chain extension reaction. The '748 patent exemplifies this type of molecule as follows: "chain-terminating analogues are based on the common nucleosides: adenosine, cytosine, guanine or inosine, thymidine or uridine. A preferred set of chain-terminating analogues are the four dideoxynucleoside triphosphates, ddATP, ddCTP, ddGTP, and ddTTP." ('748 patent, col. 24, lines 45-50).

E. Labeling and Detection of Nucleotides and Nucleic Acids

29. Scientists have developed procedures to modify nucleic acids so they can be easily detected and measured. These modification procedures include physically binding, incorporating,, or covalently binding labels to nucleic acids.

30. Many modification methods have been developed for producing labeled nucleotides and nucleic acids. These include the development of both isotopic and non-isotopic labels and labeling methods. Labels can be incorporated by substitution of an existing atom, or labels can be covalently bonded to various positions on a nucleotide's sugar, phosphate, and base moieties and then the labeled nucleotide incorporated into a nucleic acid molecule. Alternatively, a nucleic acid can be labeled using a chemically activated label.

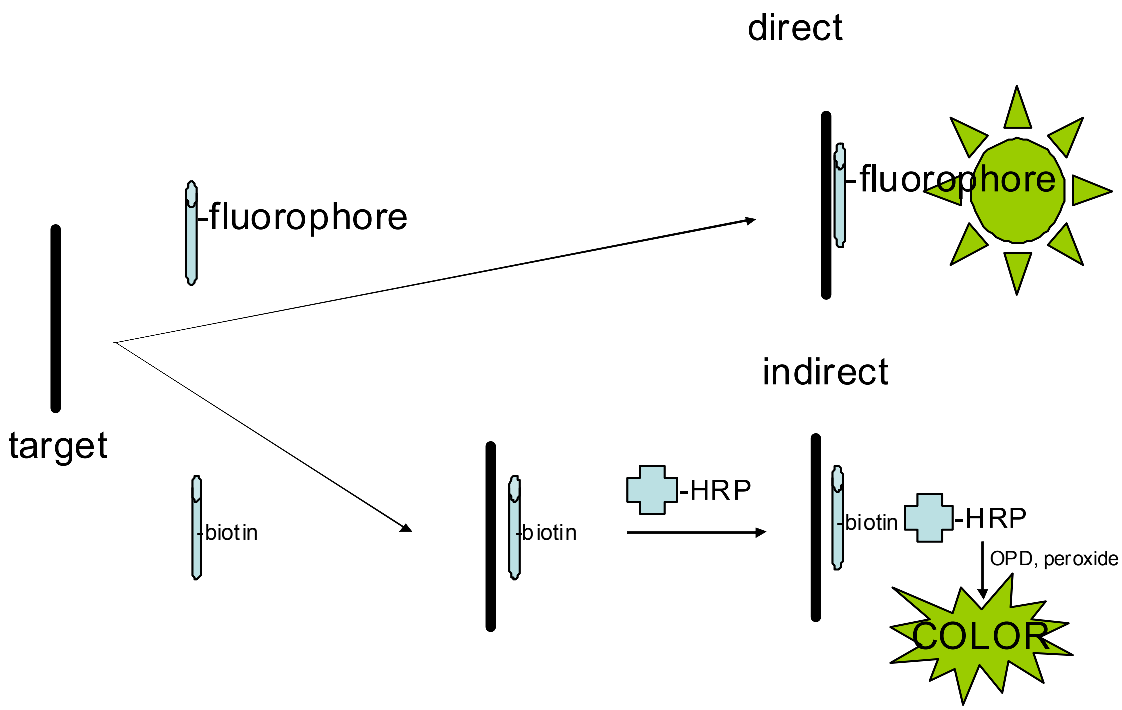


Figure 5. Direct and indirect detection schemes for DNA. A. Direct detection using a fluorophore labeled DNA probe. B. Indirect detection using a probe labeled with the indirect (or secondary label) biotin. This label is detected by specific binding to a streptavidin (SAV) molecule labeled with the enzyme, horseradish peroxidase (HRP), that is in turn detected colorimetrically by reaction with hydrogen peroxide and ortho-phenylenediamine (OPD).

31. In general, the labeling and detection of nucleic acids can be described as either "direct" or "indirect." "Direct labeling" generally refers to the modification of a nucleic acid by physically binding, incorporation or covalently binding of labels directly to a nucleic acid, allowing the nucleic acid to be directly detected. In contrast, the term "indirect labeling" refers to the modification of a nucleic acid, for example by the covalent binding of a label (indirect or secondary label) that does not itself provide a readily detectable characteristic. Instead, an indirect label provides an attachment point that is specifically recognized by a secondary chemical agent or molecule, which is itself directly detectable. The secondary binding agent is rendered detectable by attaching a label. When the detectable secondary agent binds with the indirect label, the resultant indirectly labeled nucleic acid:labeled secondary binding agent complex is detectable by virtue of the label attached to the secondary binding agent and the nucleic acid is detected "indirectly." Alternatively, the hybrid formed by the target and probe can be recognized by a labeled binding

agent (e.g., antibody specific for DNA:RNA hybrids).

32. **Direct labeling:** Direct labels can be broadly classified into isotopic and non-isotopic labels.

33. Direct labeling of a nucleic acid can be achieved by a variety of modification procedures, including substitution of an existing atom by the same atom but with different properties (e.g., ^{15}N, ^{32}P) or another atom (e.g., ^{35}S), physical binding of a molecule, or covalent attachment of another atom or molecule to an appropriate site on the molecule. One may also use a linker interposed between the label and nucleic acid. (Prober JM. Trainor GL. Dam RJ. Hobbs FW. Robertson CW. Zagursky RJ. Cocuzza AJ. Jensen MA. Baumeister K. A system for rapid DNA sequencing with fluorescent chain-terminating dideoxynucleotides. Science 1987; 238:336-41).

34. **Isotopic Labeling:** One of the earliest labels for a nucleic acid was a radioactive isotope of phosphorus, ^{32}P. This is detectable using instruments that detect radiation (Hershey AD, Chase M. Independent functions of viral protein and nucleic acid in growth of bacteriophage. J Gen Physiol 1952;36:39-56). Labeling using a radioactive label such as ^{32}P is accomplished by replacing a non-radioactive phosphorus atom, ^{31}P, in a nucleic acid with the radioactive phosphorus atom. Radioactive labels are particularly suited to labeling DNA because the substitution of a radioactive atom for a non-radioactive atom has a negligible effect on the molecular properties of the nucleic acid, including the ability of the nucleic acid to participate in hybridization reactions. Heavy nitrogen, ^{15}N, has also been used as a label for DNA in order to differentiate parent from daughter DNA. (Messelson M, Stahl WF. The replication of DNA in Escherichia coli. Proc Natl Acad Sci USA 1958; 44:671-82).

35. The major problems associated with the use of radioactive labels, such as ^{32}P labels, are (1) instability and limited shelf-life of the labels due to their short half-life; (2) safety concerns over handling and disposal of radioactive material, (3) and the need for expensive and time-consuming precautions when handling radioactive labels and labeled materials.

36. **Non-isotopic Labeling:** Despite the obvious utility of radioactive labels, which are still used today, the disadvantages of using radioactive materials inspired the development of non-isotopic labels. Starting in the 1970s, researchers developed non-isotopic labels for use in

hybridization assays, often using labels that had previously been developed for use in immunoassays. Table 1 list some of the many labels used to label nucleic acids.

TABLE 1. Direct and indirect labels for labeling nucleotides and nucleic acids

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Direct labels
Isotopes – ^{3}H, ^{125}I, ^{131}I, ^{32}P, ^{14}C, ^{33}S, ^{34}S, ^{36}S
Mass labels - ^{33}S, ^{34}S, ^{36}S, metalothionein
Fluorophores – fluorescein, rhodamine, ethidium bromide
Electron dense atoms – mercury, lead, iron, osmium,
Enzymes – alkaline phosphatase, horseradish peroxidase
Chemiluminescent compounds – acridinium esters
Electrochemiluminescent compounds – ruthenium (tris bipyridyl)
Phosphors - yttriumoxisulfide + europium
Indirect labels
Biotin
Haptens - digoxigenin

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37. **Fluorophores:** Fluorescent molecules, called "fluorophores," produce a characteristic fluorescence emission when excited by incident light. This fluorescence emission can be used to detect the fluorophore attached to a compound of interest, such as a nucleic acid. Fluorescein has long been a popular fluorophore for labeling biological compounds and since at least the 1970s has been used to directly label nucleic acids.

38. **Indirect Labeling:** Indirect labeling and detection, in contrast to direct labeling and detection, involves first modifying a nucleic acid by covalent binding a label that does not itself generate a readily detectable signal and is therefore not directly detectable. For example, the compound biotin does not generate a readily detectable signal and is therefore not directly detectable. However, certain proteins (such as avidin and streptavidin) bind with great specificity to this label. If these proteins are in turn labeled with directly detectable compounds such as fluorophores, and added to a solution containing nucleic acids labeled with biotin, the presence of the nucleic acids can then be determined by using an appropriate technique to detect the fluorophore (Bayer EA, Wilchek M. The use of the avidin-biotin complex as a tool in molecular biology. Methods Biochem Anal 1980; 26:1-45).

39. An alternative to biotin as an indirect label is a hapten (e.g., digoxigenin) that is detected using a labeled specific antibody (e.g., fluorescently labeled anti-digoxigenin antibody).

(Tchen P. et al., Chemically modified nucleic acids as immunodetectable probes in hybridization experiments. Proc Natl Acad Sci 1984; 81:3466-70).

40. Yet another form of indirect labeling is based on the recognition by a labeled anti-DNA:RNA hybrid antibody of the hybrid that results from binding of a DNA molecule with a complementary RNA probe. (Coutlee F, Bobo L, Mayur K, Yolken RH, Viscidi RP. Immunodetection of DNA with biotinylated RNA probes: A study of reactivity of a monoclonal antibody to DNA:RNA hybrids. Anal Biochem 1989; 181:96-105).

41. The patents-in-suit disclose several direct and indirect labels and label detection methods.

Examples of direct labeling include:

(i) radioisotopes that are detected by autoradiography or scintillation counting, for example ^{35}sulfur ('819 patent, col. 7, lines 2-3; col. 8, lines 52-57; col. 9, lines 5-10; col. 16, lines 22-23).

(ii) chromophores that are detected by virtue of their color by absorption spectroscopy ('819 patent, col. 8, lines 52-57; col. 9, lines 5-10).

(iii) fluorophores that are detected by fluorescence spectroscopy ('819 patent, col. 9, lines 5-10).

(iv) protein moieties, for example an enzyme, that are detected by enzyme activity. ('819 patent, col. 8, lines 52-57; col. 9, lines 5-10). (A moiety is defined as "a part, portion, or share of indefinite size." (The American Heritage Dictionary of the English language, Morris W, editor, Houghton Mifflin Co., Boston. 1980, p. 845)).

(v) mass spectrometry is also cited as a labeling and detection method and this can be used to detect isotopes and other labels based on their specific mass. ('819 patent, col. 9, lines 5-10).

Examples of indirect labeling include:

(i) biotin that is attached to a dideoxynucleotide triphosphate (ddNTP) and following attachment to the end of a primer, it is detected using streptavidin-conjugated horseradish peroxidase. The peroxidase label was detected colorimetrically using an o-phenylenediamine (OPD) substrate. ('748 patent, col. 23, lines 26-38). (In the patents-in-suit, biotin is also used extensively as an affinity label to facilitate isolation and immobilization of nucleic acids and

primers) (See Figure 5 above).

(ii) indirect labeling is also described generically in the specification of the '819 patent as "a moiety to which an isotopically labeled moiety, a chromophore, a fluorophore, or a protein moiety can be attached." ('819 patent, col. 8, lines 52-57). This description encompasses an indirect labeling scheme in which the "moiety" is for example digoxigenin and the "protein moiety" would be a labeled anti-digoxigenin antibody. This usage of the word moiety broadens its meaning to include not only part but whole entities.

VII. DISPUTED CLAIM TERMS

In this section, I analyze and give my explanation and support for what I believe is a correct interpretation of the disputed terms of the patents-in-suit.

A. "in the absence of dATP, dCTP, dGTP, or dTTP" and "in absence of non-terminator nucleotides" in the '819 patent (claims 1, 43, 46, 47), and "lacks dATP, dCTP, dGTP, and dTTP" in the '744 (claim 1) and '748 patents (claim 1)

Term	Plaintiffs' Proposed Construction	Defendant's Proposed Construction
"in the absence of dATP, dCTP, dGTP, or dTTP"	"with not more than a trivial amount of dATP, dCTP, dGTP, or dTTP" An amount is "trivial" if it does not significantly affect the ability to determine nucleotide identity through single nucleotide primer extension.	"with no dATP, dCTP, dGTP, or dTTP"
"in the absence of non-terminator nucleotides"	"with not more than a trivial amount of non-terminator nucleotides" An amount is "trivial" if it does not significantly affect the ability to determine nucleotide identity through single nucleotide primer extension.	"with no non-terminator nucleotides"

Term	Plaintiffs' Proposed Construction	Defendant's Proposed Construction
"lacks dATP, dCTP, dGTP and dTTP"	"has not more than a trivial amount of dATP, dCTP, dGTP, and dTTP" An amount is "trivial" if it does not significantly affect the ability to determine nucleotide identity through single nucleotide primer extension.	"has no dATP, dCTP, dGTP, or dTTP"

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42. One of ordinary skill in the art would understand that the claim language "in the absence of" and "lacks" means "with not more than a trivial amount of" and "has not more than a trivial amount of," respectively. Consequently, the claim language "in the absence of dATP, dCTP, dGTP, or dTTP" means "with not more than a trivial amount of dATP, dCTP, dGTP, or dTTP"; the claim language "in the absence of non-terminator nucleotides" means "with not more than a trivial amount of non-terminator nucleotides"; and the claim language "lacks dATP, dCTP, dGTP, and dTTP" means "has not more than a trivial amount of dATP, dCTP, dGTP, and dTTP." In addition, one of ordinary skill in the art would understand that an amount is "trivial" in the context of the patents-in-suit if it does not significantly affect the ability to determine nucleotide identity through single nucleotide primer extension.

43. The claim language, specifications, and prosecution histories of the patents-in-suit support this interpretation. The terms "absence" and "lacks" are in the claims of the patents-in-suit in essentially two contexts. First, the claims describe the extent to which certain components exist in a mixture during a particular step. The components at issue are either "dATP, dCTP, dGTP, and/or dTTP" (often referred to collectively as "dNTPs") or non-terminator nucleotides. Claim 1 of the '819 patent describes a "contacting" step in where a duplex containing a primer is exposed to a mixture containing terminators and an "absence" of dNTPs. This corresponds to claim 1 of the '744 and '748 patents which describe a reagent composition including a primer, terminators and other components, but "lacks" dNTPs. One of ordinary skill in the art would understand that such steps are performed wherein the mixture has an "absence of" or "lacks" such components and thus the claim terms require there to not be more than a trivial amount of such components.

44. Second, the terms "absence" and "lacks" appear in connection with the identification and detection step. Claim 1 of the '819 patent, for example, describes a method that includes determining the presence and identity of a nucleotide base a specific position in a nucleic acid by performing a "detecting" step after a terminator is incorporated onto a primer. The claim requires that detection be "conducted in the absence of non-terminator nucleotides." The claim language makes clear that such steps are performed wherein the mixture has an "absence of" or "lacks" such components. Consequently, one of ordinary skill in the art would understand that these claim terms require there to be not more than a trivial amount of such components. These terms, however, do not require no presence at all of the components at issue, but rather permit some trivial amounts which do not significantly interfere with the ability to determine nucleotide identity through single nucleotide primer extension.

45. The specifications confirm that this interpretation is appropriate. The field of the claimed invention does not require complete purity of components and reagents to achieve the objectives of the claimed invention. Instead, one of ordinary skill in the art would understand, as reflected in examples in the specifications, that some trivial amounts of unnecessary or undesirable components are typically present.

46. Examples in the specification demonstrate that reagents and components used with the claimed inventions are not 100% pure. For example, Figures 1A-1C show an autoradiogram of labeled DNA. The specifications explain that these figures show "minor bands" or "background" or "noise" which reflect experimental conditions that are not 100% pure but are caused by the presence of contaminants:

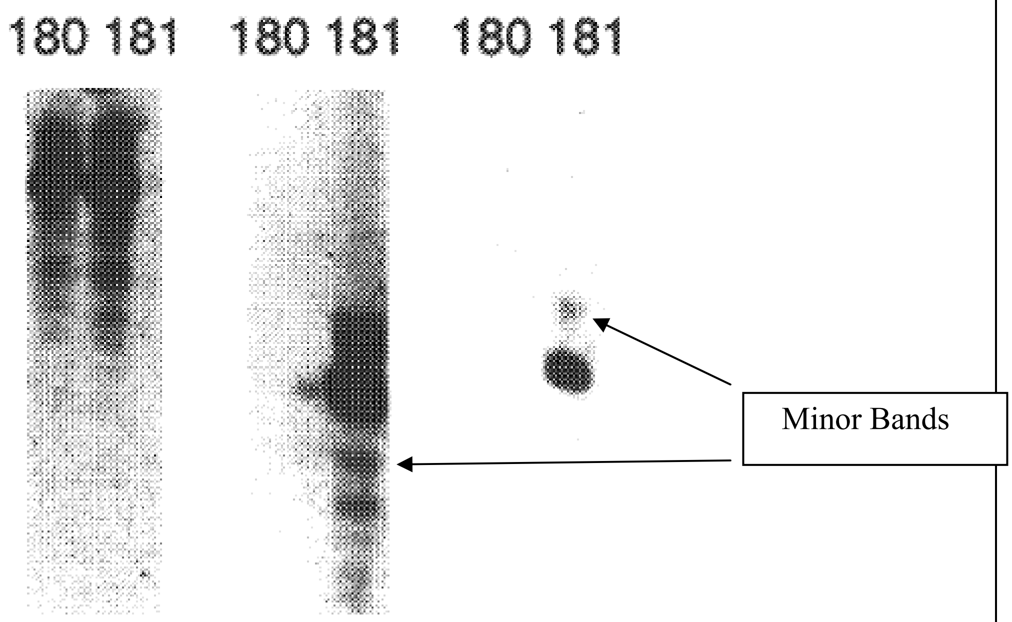


FIG. 1A FIG. 1B FIG. 1C

When discussing Figures 1A-1C, the specifications state "[t]he minor bands above and below the main band are presumably contaminants due to incomplete reactions or side reactions that occurred during the step-wise synthesis of the oligonucleotide." ('819 patent, col. 6, lines 44-47). Figure 1B has minor bands which are contaminants. Figure 1C also shows a minor band even though the products used for that experiment were purified.

47. The specifications also describe experimental data that confirm the purification methods described in the specifications do not remove all contaminants. Example 2 in the specifications describes a washing procedure using magnetic beads ("Dynabeads") to remove nucleotides from a mixture. The specifications explain that the washing procedure does not remove each and every nucleotide, but rather results in a "nonspecific label" of approximately 3-4% which was probably caused by "unincorporated nucleotides that were not completely removed by the washing step." ('819 patent, col. 17, line 54-col. 18, line 35).

48. The preferred embodiment described in the '819 patent describes several steps used to practice the claimed invention. First, a sample of DNA is obtained for analysis. ('819 patent, col. 21, lines 26-33). Second, the DNA sample is "amplified" to create a larger number of copies of

the DNA, to facilitate analysis in subsequent steps. ('819 patent, col. 21, lines 32-37). The amplification step requires that the DNA be added to a mixture that contains, among other things, dNTPs. The dNTPs are incorporated onto growing DNA strands as part of the amplification process. Third, the amplified DNA is purified by binding the DNA to magnetic beads (Dynabeads) and then washing the amplified DNA (the washing step) in the same manner as described above in Example 2. ('819 patent, col. 21, lines 38-51). One of ordinary skill in the art would understand the objective of this washing step is to remove dNTPs and other contaminants from the mixture. Finally, the resulting purified DNA is used in subsequent single base extension primer extension reactions to identify the nucleotide of interest in the DNA. ('819 patent, col. 21, line 52 – col. 22, line 55). This same procedure is described in the embodiments of the '744 and '748 patent. ('744 patent, col. 17, lines 46-56, '748 patent, col. 17, lines 34-59).

49. In view of the experimental results described in Example 2, in which not all "unincorporated nucleotides" were removed from the mixture using a Dynabead washing step, one of ordinary skill in the art would understand that not all dNTPs (which are also nucleotides) would be removed with the same Dynabead washing step described in the preferred embodiment. In other words, trivial amounts of dNTPs would remain in the mixture. Despite this fact, the specifications explain that one is able to identify a nucleotide base of interest with the preferred embodiment of the '819 patent. In particular, the specifications state that "[b]y suitably matching of the measured spectra to this library of canonical emission spectra it is possible to identify which chain-terminating nucleotide(s) have been added to the 3'terminus of the primer and thereby identify the nature of the sequence polymorphism in the template." ('819 patent, col. 22, lines 47-51).

50. The specifications describe experiments in which a nucleotide base of interest is successfully identified even when contaminants are present. Figure 4 shows bands created by primers that have been extended by labeled terminators. The description of Figure 4 discloses that labeling occurs "predominantly" in one of the lanes in the figures. One of ordinary skill in the art would understand that this "predominant" lane uncovers the nucleotide identity despite the presence of minor bands. ('819 patent, Figure 4 and col. 7, lines 4-22). Contaminants are present even though the "labeled primer DNA was released from the **washed** beads…." ('819 patent, col. 7,

lines 10-14 (emphasis added)).

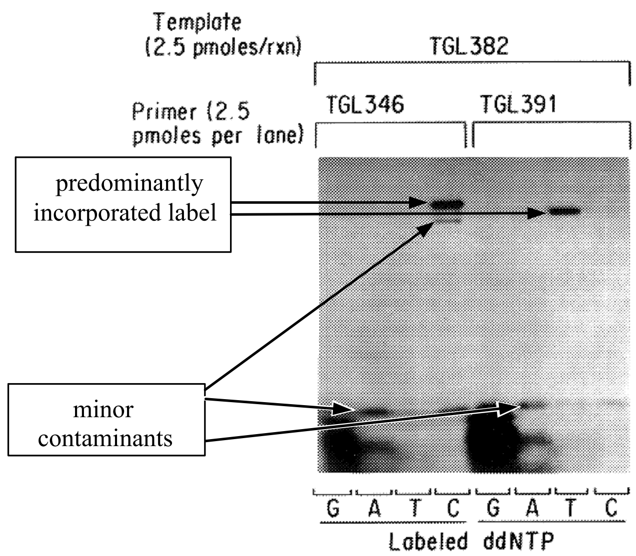
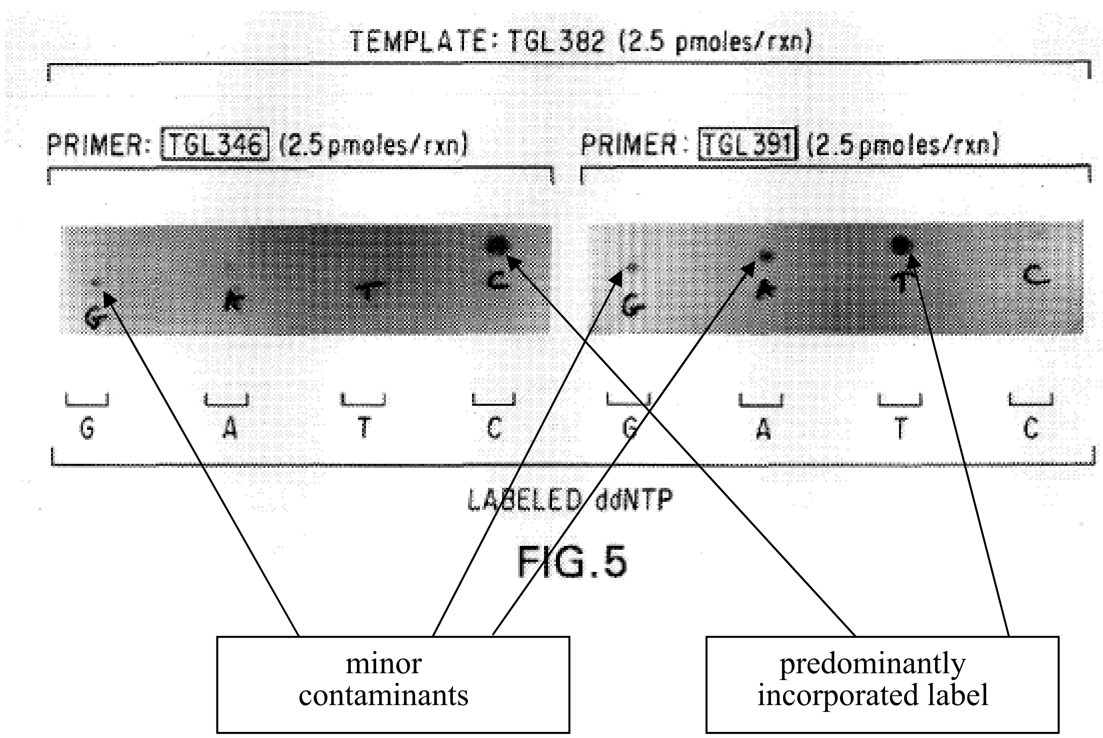


FIG.4

51. Nucleotide identity can be determined by analyzing Figure 5 in the specifications even though it shows the presence of some contaminants which result in visible dots associated with more than one nucleotide base. One of ordinary skill in the art would use the location of the predominant label to determine nucleotide identity. (('819 patent), col. 7, lines 23-30)



52. One of ordinary skill in the art, upon reviewing Figure 5 and its associated text, would understand that the predominantly labeled nucleotide is represented by the darkest dots in Figure 5. These dots correspond to the "C" nucleotide on the left side of the figure and the "T" nucleotide on the right side of the figure.

53. Figure 8 also depicts autoradiographic analysis to analyze samples of DNA for the nucleotide of interest. One of ordinary skill in the art would be able to determine nucleotide identity by analyzing Figure 8 in the specification. For example, by looking at the top autoradiograph labeled "magnetic beads," the predominant result (for individual ESB164) corresponds to the nucleotide base guanosine (G). There are contaminants that are seen in the other lanes. All of the autoradiograms in the upper panel of this figure show some sort of minor contaminant or background.

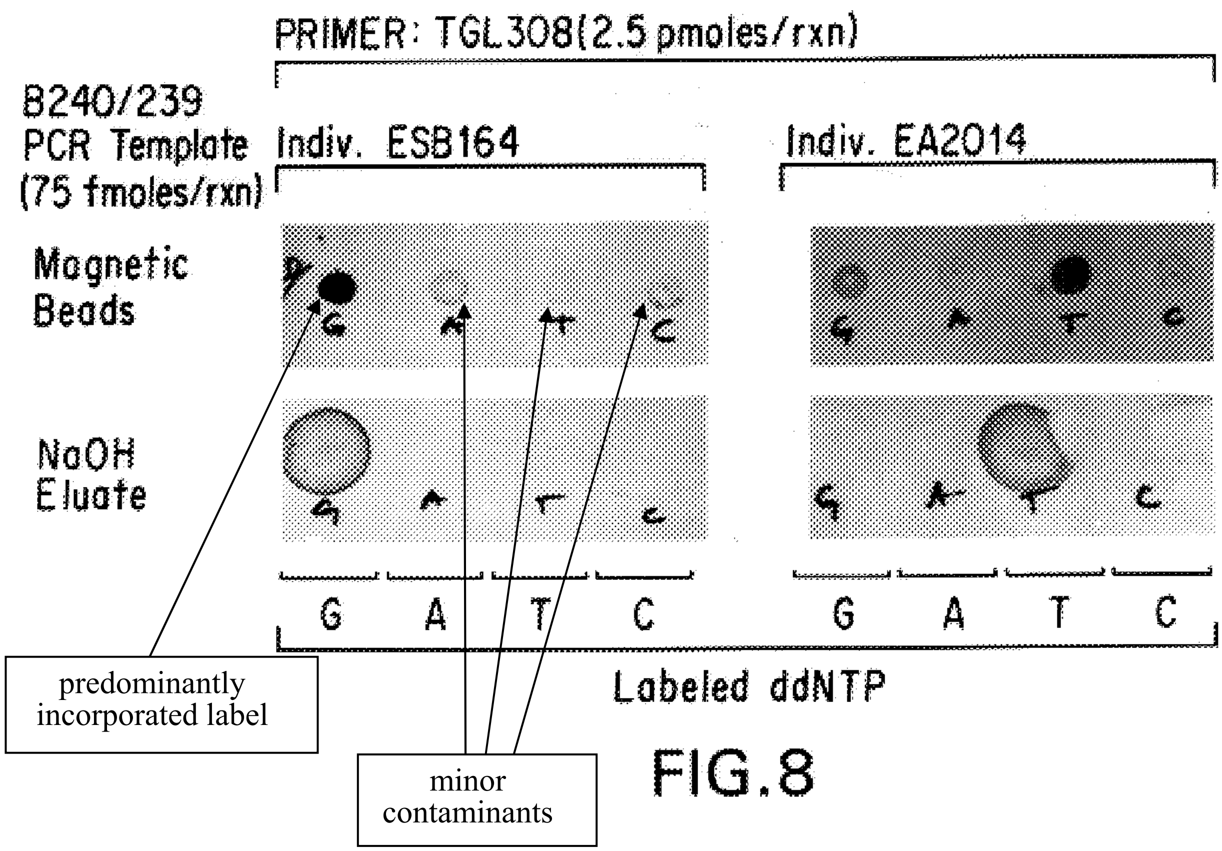


FIG.8

54. Other references show that background effects (e.g. contaminants such as dNTPs) are typically expected in the field. For example, a paper by Syvanen reports results of extension reactions performed using an amplified nucleic acid sample immobilized to the inside surface of a plastic microwell and tritiated dNTPs. A very small signal above background was observed in control experiments using water as the sample instead of a nucleic acid (Syvanen AC. Detection of point mutations in human genes by the solid-phase minisequencing method. Clin Chim Acta 1994; 226: 225-236 – see Table 2, p. 229). Another example is also shown in an earlier paper by Syvanen. In that instance, the data from analogous water control reactions reveals a variable background presumably attributable to non-specific binding of the ^{35}sulfur-dTTP and ^{35}sulfur-dCTP from the assay mixture (Syvanen AC. Aalto-Setala K. Harju L. Kontula K. Soderlund H. A primer-guided nucleotide incorporation assay in the genotyping of apolipoprotein E. Genomics. 1990;8:684-92, see Table 3, p. 689). Background readings were also observed in a similar experiment using ^{3}hydrogen-labeled dTTP and ^{32}phosphorus-labeled dCTP (Table 4, p. 690). One of ordinary skill in the art would not expect all contaminants to be removed but would consider experiments to be successful, even with contaminants, as long as the experiment resulted in data that was well-above background.

55. Although reagent mixtures may contain trivial amounts of undesirable components, one of ordinary skill in the art would understand that such amounts are permissible as long as the primary goal of the claimed inventions, to identify a nucleotide using single base primer extension, is not significantly affected. The prosecution histories are consistent with the above interpretation of the claim language.

56. The accuracy of Plaintiffs' proposed construction is confirmed by the patent file history. In the initial patent application, the claims did not include a limitation relating to the absence of dNTPs or non-terminator nucleotides. ('819 File History at BCI000186-99). The Patent Office, however, subsequently rejected the initial claims. (*Id.* at BCI000254-262). The rejections were based on references which described compositions that required dNTPs be present. (*Id.* at BCI000289). However, one of ordinary skill in the art would understand that the claimed inventions of the patents-in-suit did not require the presence of dNTPs. In its response, at the

suggestion of the patent examiner, the applicant amended the claims to include a "substantial absence" of dNTPs, so as to distinguish the claims of the pending patent application from the asserted references. (*Id.* at BCI000284 ("The present claims are believed to embody the suggestions of the Examiners.")).

57. Later, the applicant subsequently amended the claims and removed the word "substantial." (*Id.* at BCI000322-25). This amendment changed the claims from requiring a "substantial absence" of dNTPs (i.e., absence to a considerable degree) to simply an "absence" of dNTPs (i.e., not more than a trivial amount).

58. The prosecution histories are consistent with Plaintiffs' proposed construction which recognizes that "absence" and "lacks" permit no more than a trivial amount of dNTPs and non-terminator nucleotides. The prosecution histories show that a key difference between the claims of the patents-in-suit, and the prior art references, is that the prior art references required the presence of dNTPs, whereas the claims of the patents-in-suit do not. ('819 File History at BCI000289; '744 File History at BCI000958, BCI000961, BCI001010, BCI001016, BCI001019; '748 File History at BCI001503).

59. I disagree with Defendant's proposed constructions of these claim terms, which I understand are as follows: "in the absence of dATP, dCTP, dGTP, or dTTP" means "with no dATP, dCTP, dGTP, or dTTP"; "in the absence of non-terminator nucleotides" means "with no non-terminator nucleotides"; and "lacks dATP, dCTP, dGTP, and dTTP" means "has no dATP, dCTP, dGTP, and dTTP."

60. Defendant's proposed constructions do not take into account that there are no specific instructions in the specifications or claims to remove every last molecule of dNTPs or non-terminator nucleotides, and thus are inconsistent with the fact that "absence" and "lacks" can encompass trivial amounts of dNTP or non-terminator nucleotides that may be left in the final reaction mixture. Such trivial amounts would not significantly affect the ability to determine nucleotide identity through single nucleotide primer extension. As discussed above, the basis for this acceptance of trivial amounts is the appreciation that impurities may be present in components of the reaction mixture (e.g., PCR amplified template) and that these may persist via non-specific

binding to assay components, such as the magnetic beads used to capture the biotinylated components and on which the primer:template hybrid is formed. Example 2 in specifications reveals that non-specific binding of labeled dideoxynucleotides can occur ('819 patent, col.17, line 55- col.18, line 34). In addition the preferred embodiment and other examples in the specifications demonstrate that trivial amounts of contaminants may be present. Under Defendant's proposed construction, however, such contaminants are not permissible.

B. "detectable marker" ('819 patent, claims 29, 43, 46; '744 patent, claim 3-5; '748 patent, claim 3-5) and "detectable label" ('819 patent, claims 3, 45)

Term	Plaintiffs' Proposed Construction	Defendant's Proposed Construction
"detectable marker" "detectable label"	"a moiety which permits discovering the presence or existence of a specific nucleic acid or nucleic acid sequence using autoradiography or scintillation counting, fluorescence or absorption spectroscopy, mass spectrometry, enzyme activity, or other methods"	"a moiety, the identity of which is determined using the moiety's distinguishable properties, and which is attached to a terminator"

61. One of ordinary skill in the art would understand that the claim language "detectable marker" and "detectable label" means "a moiety which permits discovering the presence or existence of a specific nucleic acid or nucleic acid sequence using autoradiography or scintillation counting, fluorescence or absorption spectroscopy, mass spectrometry, enzyme activity, or other methods."

62. A label (also known as a marker) is anything that functions as a means of identification (American Heritage Dictionary of the English language, Morris W, editor, Houghton Mifflin Co., Boston. 1980, p. 730) and as discussed above in Section VI.E it can have properties that make it either directly or indirectly detectable. Thus, one of ordinary skill in the art when reading the patents-in-suit would understand that "detectable marker" and "detectable label" have the same meaning.

63. The specifications of the patents-in-suit demonstrate that a "detectable marker" or "detectable label" is a moiety that permits a specific nucleic acid or nucleic acid sequence to be

detected. ('819 patent, col. 8, lines 52-59; col. 9, lines 5-14; col. 10, lines 15-22; '744 patent, col. 9, lines 8-14; col. 9, lines 52-61; col. 15, line 60- col. 16, line 5; '748 patent, col. 9, lines 9-15; col. 9, lines 52-62, col. 15, line 60 – col. 16, line 6).

64. The specifications describe several examples in which a "detectable marker" or "detectable label" is used to discover the presence or existence of specific nucleic acids or nucleic acid sequences, when the detectable marker or label is used to label a terminator which is incorporated into an extended primer. For example, Figure 4 in the patents-in-suit is an autoradiogram of two sets of four reactions with the four different isotopically labeled ddNTPs (^{35} sulfur-ddNTPs) and a mixture that included the nucleic acid strand and the primer. Once hybridization of the primer and the nucleic acid molecule occurs, the correct, matching isotopically labeled ddNTPs can pair with the nucleotide of interest and be incorporated onto the end of the primer. Detecting the nucleotide of interest is performed through autoradiography (resulting in Figure 4) which shows that for sample TGL 346, the nucleotide of interest is a C and for sample TGL 391, the nucleotide of interest is T. ('819 patent, col. 7, lines 4-22).

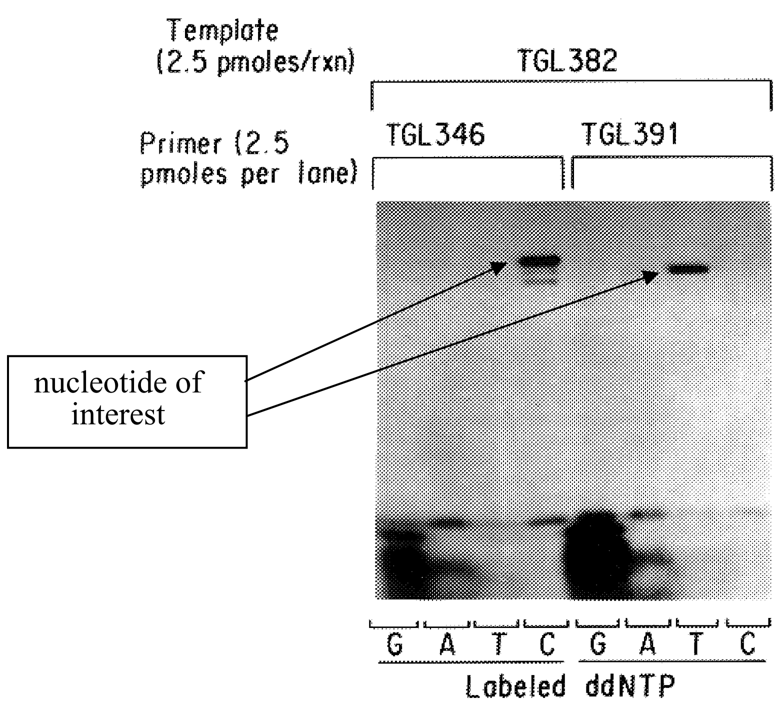


FIG.4

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65. Figure 7, and its accompanying Example 5 discussed in the specifications, show a "detectable marker" or "detectable label" is used to discover the presence or existence of specific nucleic acids or nucleic acid sequences, when the detectable marker is used to label a terminator which is incorporated into the primer. One of ordinary skill in the art would understand that for individual EA2014 the nucleotide of interest is a "A," which means that "ddTTP" was the radiolabeled terminator that bound to the nucleic acid molecule.

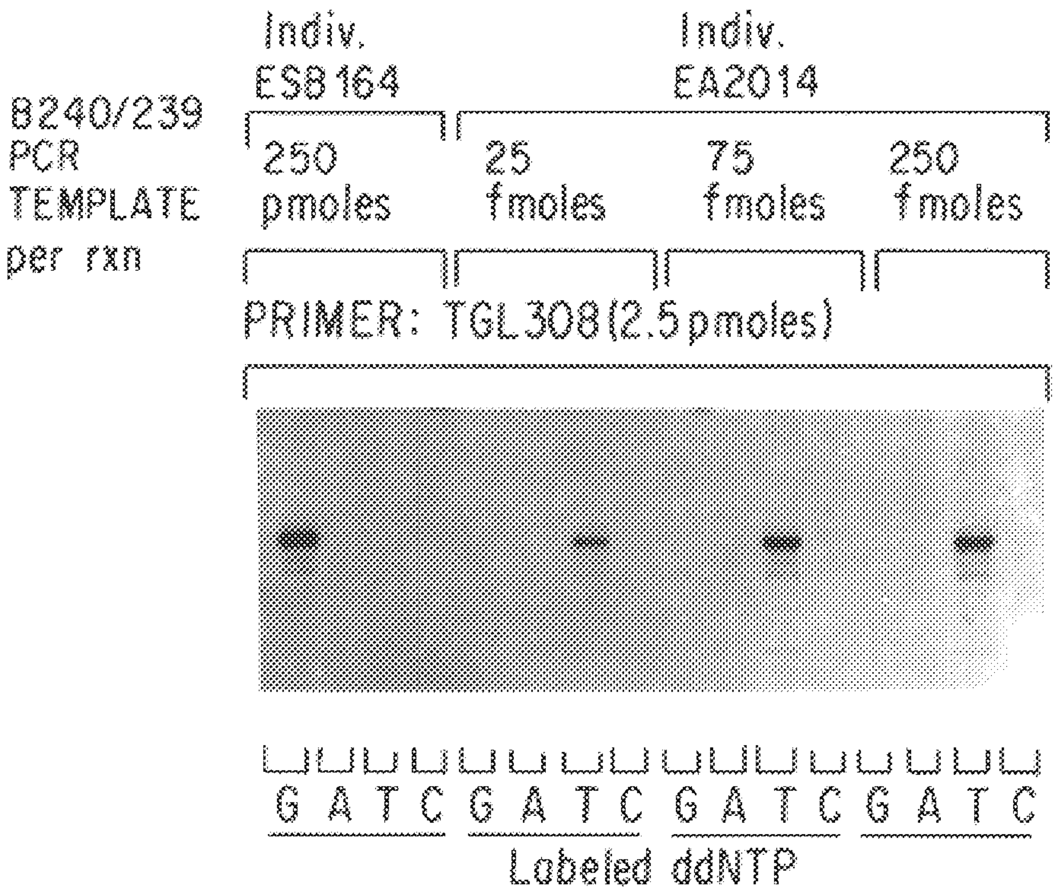

FIG.7

66. One of ordinary skill in the art would understand the specifications do not limit the way in which the marker or label may be detected, but rather provide several examples of possible detection systems. The specifications disclose a variety of detection systems including

autoradiography or scintillation counting, fluorescence or absorption spectroscopy, mass spectrometry, and enzyme activity. ('819 patent, col. 9, lines 5-10; '744 patent, col. 9, lines 52-58; '748 patent, col. 10, line 39 – col. 11, line 9). There are a variety of other detection systems, in addition to the methods listed in this paragraph (see Section VI.E. described above). Thus, one of ordinary skill in the art would understand a "detectable marker" or "detectable label" may be detected through other suitable methods as well.

67. I disagree with Defendant's proposed construction of "detectable marker" and "detectable label," which I understand is "a moiety, the identity of which is determined using the moiety's distinguishable properties, and which is attached to a terminator." Defendant's proposed construction is incorrect because it includes several restrictions which are not required by the claim language, including the requirement that the identity of the marker or label being determined using "the moiety's distinguishable properties," and that the moiety must be "attached" to a terminator. As explained above, the claim language and specifications do not restrict the manner in which the marker or label may be detected, and certainly do not require that they be detected solely using the moiety's "distinguishable properties." Similarly, there is no requirement found in the claims or specifications that the marker or label must be "attached" to the terminator. This requirement is too narrow because, by use of the term "attached," it might suggest that only one form of modification is encompassed, i.e., attachment. Defendant's proposed construction is flawed because, among other things, it does not encompass the incorporation type of modification in which an existing atom is substituted by another atom with detectable properties (e.g., replacement of ^{31}P with ^{32}P in the phosphate part of a nucleotide or replacement of oxygen with ^{35}S in the phosphate part of a nucleotide ('819 patent, col. 7, lines 2-3)) or other labeling methods described in the specifications of the patents-in-suit and/or others that were known in the art. See ¶¶ 77-89, below.

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C. "terminator" ('819 patent, claims 1, 3, 43, 46, 47; '744 patent, claims 1-7, 9; '748 patent, claims 2-7); "nucleotide terminators, or terminator nucleotide analogs" ('748 patent claim 1)

Term	Plaintiffs' Proposed Construction	Defendant's Proposed Construction
"terminator"	"a nucleotide or nucleotide analog which, after being incorporated onto the 3' end of a primer, does not permit any further extension of the primer"	"a molecule, including a nucleotide, nucleotide analog, dideoxynucleotide, or arabinoside triphosphate, that when incorporated onto the 3' end of a primer is capable of specifically terminating the extension reaction and inhibiting further elongation"
"nucleotide terminators, or terminator nucleotide analogs"	"nucleotide terminators, or terminator nucleotide analogs" means "nucleotides or nucleotide analogs which, after being incorporated onto the 3' end of a primer, do not permit any further extension of the primer"	"a molecule, including a nucleotide, nucleotide analog, dideoxynucleotide, or arabinoside triphosphate, that when incorporated onto the 3' end of a primer is capable of specifically terminating the extension reaction and inhibiting further elongation"

68. A person of ordinary skill in the art would understand that the term "terminator" means "a nucleotide or nucleotide analog which, after being incorporated onto the 3' end of a primer, does not permit any further extension of the primer." Similarly, person of ordinary skill in the art would understand that the term "nucleotide terminators, or terminator nucleotide analogs" means "nucleotides or nucleotide analogs which, after being incorporated onto the 3' end of a primer, do not permit any further extension of the primer."

69. Terminators were well known as of 1991 and prominent examples were the dideoxynucleotides (Prober JM. Trainor GL. Dam RJ. Hobbs FW. Robertson CW. Zagursky RJ. Cocuzza AJ. Jensen MA. Baumeister K. A system for rapid DNA sequencing with fluorescent chain-terminating dideoxynucleotides. Science 1987; 238:336-41; Brown TA. DNA Sequencing. The basics. Oxford:IRL Press, 1994, pp. 3-5, 41, 94; Sambrook J, Fritsch EF, Maniatis T. Molecular cloning. A laboratory manual. Cold Spring Harbor: Cold Spring Harbor Laboratory Press, 2nd edn, 1989, p. 13.6; King RC, Stansfield WD. A dictionary of genetics. Oxford: Oxford

University Press, 5th edn, 1997, pp. 57 and 98).

70. The term "nucleotide terminators" refers to terminators that are members of the class of compounds known as nucleotides. Terminators are a class of compounds that include nucleotides, and they have the common property of terminating a polymerase-catalyzed 3'-extension of a nucleic acid. Similarly, the term "terminator nucleotide analogs" refers to nucleotide analogs that are terminators, i.e., they have the property of terminating a polymerase-catalyzed 3'-extension of a nucleic acid.

71. Plaintiffs' proposed construction is supported by the specifications. One of ordinary skill in the art would understand that the purpose of the invention is to identify a nucleotide base by, among other things, extending a primer by a single terminator. The specification and the claims repeatedly teach that the invention involves primer extension by a single base (terminator):

- "The net result is that the oligonucleotide primer has been <u>extended by one terminator</u>." ('819 patent, at col. 5, lines 51-53).
- "The net result is that the oligonucleotide primer has been <u>extended by one terminator</u>." ('819 patent, at col. 9, lines 46-47).
- "[T]he current invention will generate a discrete molecular species <u>one base longer</u> than the primer itself." ('748 patent, at col. 4, lines 12-15).
- '819 patent, claims 1(c), 43(c), 46(c) and 47(c) all state in the claims that a complementary terminator incorporates onto the 3' end of the primer "to thereby extend said 3' end of said primer by one terminator." ('819 patent, col. 30, lines 50-51, col. 33, lines 48-49, col. 34, lines 40-41, col. 36, lines 6-7).

Thus, one of ordinary skill in the art would recognize that a key requirement of the invention is that the extension reaction terminates upon incorporation of a single terminator.

72. The embodiments described in the specifications also support Plaintiffs' position that the primer should be extended by only one terminator. For example, the preferred embodiment of the '819 patent describes incorporation of a single terminator with no subsequent primer extension. ('819 patent, at col. 22, lines 47-51 and col. 21, lines 57-65). None of the embodiments in the patents-in-suit disclose a primer extension reaction <u>after</u> a terminator has been incorporated onto the

3' end of the primer.

73. I disagree with Defendant's proposed construction of "terminator," which I understand is "a molecule, including a nucleotide, nucleotide analog, dideoxynucleotide, or arabinoside triphosphate, that when incorporated onto the 3' end of a primer is capable of specifically terminating the extension reaction and inhibiting further elongation." Defendant's construction is incorrect because it does not require the terminator to actually "terminate" the primer extension reaction after the terminator is incorporated onto the 3' end of the primer.

D. "labeled with a detectable marker" ('819 patent, claims 28, 29)

Term	Plaintiffs' Proposed Construction	Defendant's Proposed Construction
"labeled with a detectable marker"	"modified with a moiety which permits discovering the presence or existence of a specific nucleic acid or nucleic acid sequence using autoradiography or scintillation counting, fluorescence or absorption spectroscopy, mass spectrometry, enzyme activity, or other methods"	Claims 28 and 29 are indefinite

74. One of ordinary skill in the art would understand the claim term "labeled with a detectable marker" means "modified with a moiety which permits discovery of the presence or existence of a specific nucleic acid or nucleic acid sequence using autoradiography or scintillation counting, fluorescence or absorption spectroscopy, mass spectrometry, enzyme activity using a protein moiety, or other methods."

75. For the reasons described above in Section VII.B, a "detectable marker" should be construed to mean "a moiety which permits discovering the presence or existence of a specific nucleic acid or nucleic acid sequence using autoradiography or scintillation counting, fluorescence or absorption spectroscopy, mass spectrometry, enzyme activity, or other methods."

76. Additionally, for the reasons set forth below, one of ordinary skill in the art would understand that a terminator that is "labeled with a detectable marker" is a terminator that has been modified with a detectable marker, i.e., with a moiety which permits discovery of the presence or

existence of a specific nucleic acid or nucleic acid sequence using autoradiography or scintillation counting, fluorescence or absorption spectroscopy, mass spectrometry, enzyme activity using a protein moiety, or other methods.

77. As discussed above in Section VII.B, the specifications support Plaintiffs' proposed construction. The specifications teach that several labeling techniques can be used in connection with the claimed invention:

> Several approaches can be used for the labeling and detection of terminators: (1) radioactivity and its detection by either autoradiography or scintillation counting, (2) fluorescence or absorption spectroscopy, (3) mass spectrometry, or (4) enzyme activity, using a protein moiety.

('819 patent, at col. 9, lines 5-10).

78. As explained below, one of ordinary skill in the art would understand that each of the labeling techniques described above involves modifying an item (e.g., terminator) so that it is detectable.

79. Radioactivity: A terminator could be labeled with radioactivity by replacing one atom in the terminator with a radioactive version of the same atom. The decay of radioactive isotopes, such as ^{35}sulfur can be detected by either autoradiography or scintillation counting. ('819 patent, col.9, lines 5-10).

80. Fluorescence or absorption spectroscopy: An inherent property of the label may be revealed by a secondary process. For example, exposure of a fluorophore label such as fluorescein ('819 patent, col. 9, lines 5-10) to incident radiation causes the fluorescein label to produce an intense yellow-green light emission that can be observed visually or measured by fluorometry. The specifications disclose labeling using a fluorescent marker "where each of the four ddNTPs has been modified by attachment of a different fluorescent reporter group." ('819 patent, at col. 22, lines 13-18). Another technique would be to detect a label directly detectable by eye due to an inherent color or the color may be measured by absorption spectroscopy. ('819 patent, col. 9, lines 5-10). As a result, one of ordinary skill in the art would understand that a terminator could be labeled for use in fluorescence or absorption spectroscopy by modifying the terminator by attaching a fluorescent or absorptive marker to it.

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81. Enzyme activity: Protein molecules are used extensively as labels, and are detected by virtue of their enzyme activity. (‘819 col. 9, lines 4-9). For example, an alkaline phosphatase label can be detected and measured via an alkaline phosphatase catalyzed conversion of a non-fluorescent 4-methylumbelliferone substrate, to a highly fluorescent 4-methylumbelliferone product.

82. Mass spectrometry: Mass spectrometry is another technique used to detect labels. (‘819 patent, col. 9, lines 5-10) It is the mass characteristic of the label that underlies its detectability (see below).

83. One of ordinary skill in the art would also understand that a terminator could be mass-labeled for use in mass spectrometry by modifying the terminator’s mass in some fashion, whether it be by replacing an atom with another atom or molecule with a different mass, attaching an atom or molecule to the terminator, or performing some other modification which sufficiently changes the mass of the terminator to render it readily detectable by mass spectrometry.

84. It was recognized as early as the 1950s that a broad class of labels are substances that can be detected by mass spectrometry and, by the time the initial application for the patents-in-suit was filed in 1991, mass spectrometry was already known to be useful in the context of labeling and detecting nucleic acids.

85. Mass spectrometry is an analytical technique for the determination of the elemental composition of a sample or molecule by measurement of mass. In mass spectrometry chemical compounds are ionized to generate charged molecules or fragments that are then detected and measured based on their characteristic mass-to-charge ratios. This allows the isotopic composition of elements in a molecule to be determined.

86. In a nucleic acid application, mass labels have been used to label nucleic acid bases – For example:

- adenosine labeled with deuterium (Shaw SJ, Desiderio DM, Tsuboyama K, McCloskey JA. Mass spectrometry of nucleic acid components. Analogs of adenine. J Am Chem Soc 1970; 92:2510-22),
- thymine and uracil derivatives labeled with ^{18}oxygen (Wang SY, Hahn BS, Fenselau C,

Zafiriou OC. Enrichment of ^{18}O in the nucleic acid bases. Biochem Biophys Res Commun 1972; 48:1630-5),

- aminoacyl-tRNA labeled by ^{15}nitrogen and ^{13}carbon leucine (Watt PW, Lindsay Y, Chien PAF, Gibson JNA, Taylor DJ, Rennie MJ. Isolation of amino acyl tRNA and its labeling with stable isotope tracers: use in studies of human tissue protein synthesis. Proc Natl Acad Sci 1991; 88:5892-6),
- ^{13}carbon and di-pentafluorobenzyl electrophore label for a guanine derivative (Fedtke N, Boucheron JA, Turner MR Jr, Swenberg JA. Carcinogenesis 1990; 11:1279-85;
- pentafluorobenzyl and cinnamoyl electrophore labels for nucleosides (Trainor TM, Giese RW, Vouros P. Mass spectrometry of electrophore-labeled nucleosides. Pentafluorobenzyl and cinnamoyl derivatives. J Chromatogr 1988; 452:369-76), and
- a ^{13}carbon label for uracil (Strong JM, Anderson LW, Monks A, Chisena CA, Cysyk RL. A ^{13}C tracer method for quantitating de novo pyrimidine biosynthesis in vitro and in vivo. Anal Biochem 1983; 132:243-53).

87. Mass labels have also been exploited in the context of nucleic acid sequencing (Mills RL. Genomic sequencing methods. US Patent 1991:5,064,754; Brennan T, Chakel J, Bente P, Field M. New methods to sequence DNA by mass spectrometry. Biological mass spectrometry. Burlingame AL, McCloskey, eds, Amsterdam:Elsevier, 1990, p 159-77; Brennan T, Chakel J, Bente P, Field M. New methods to sequence DNA by mass spectrometry. SPIE 1990;1260:60-77). In one study presented at a conference in San Francisco in 1989, each of the four ddNTP terminators was labeled (or marked) with a stable isotope of sulfur (as the alpha-thio triphosphate) to give four differently atomic labeled terminators: ddATP-^{32}sulfur, ddGTP-^{34}sulfur, ddCTP-^{33}sulfur, and ddTTP-^{36}sulfur (Brennan T, Chakel J, Bente P, Field M. New methods to sequence DNA by mass spectrometry. SPIE 1990;1260:60-77; Brennan TM. Determining DNA sequences by mass spectrometry. US Patent 1991:5,0003,059). The four differently labeled terminators were used instead of fluorescently-labeled terminators in a Sanger sequencing reaction. The various sulfur-labeled terminated fragments were separated by capillary electrophoresis and the separated fragments processed for detection in a mass spectrometer. The fragment was incinerated to produce

sulfur dioxide and the mass of the sulfur dioxide is characteristic of the labeled terminator in the fragment – fragments terminated with ddATP-^{32}sulfur produce ^{32}sulfur -sulfur dioxide that has a mass of 64, whereas sulfur dioxide from ddGTP-^{34}sulfur, ddCTP-^{33}sulfur, and ddTTP-^{36}S has a mass of 66, 65, and 68, respectively. These differences are easily distinguished by the mass spectrometer.

88. There were also other labeling approaches known in the art at the time of the invention. Consequently, one of ordinary skill in the art would understand the claimed invention is not limited to a specific labeling or modification technique, but rather may be used with any labeling approach which permits suitable detection for use with the claimed invention.

89. The following references for example, disclose a variety of labels used in the context of nucleic acid labeling:

- isotopes of tin (Arlinghaus HF, Spaar MT, Thonnard N, McMahon AW, Jacobson KB. Applications of resonance ionization spectroscopy for semiconductor, environmental and biomedical analysis. SPIE 1991;1435:26-35); and
- iron and rare earths (Jacobson KB, Arlinghaus HF, Buchanan MV, Chen C-H, Glish GL, Hettich RL, McLuckey SA. Applications of mass spectrometry to DNA sequencing. GATA 1991;8:223-9;8:223-9; Hunkapillar et al. Large-Scale and Automated DNA Sequence Determination. Science 1991;254:59-67)

90. I disagree with Defendant's contention that "labeled with a detectable marker" is indefinite. Defendant, however, has not disclosed the basis for this position. In any event, the phrase is not indefinite. For the reasons described above, one of ordinary skill in the art would construe this language in the manner proposed by Plaintiffs.

E. "labeled terminator" in the '819 patent (claims 3 and 45)

Term	Plaintiffs' Proposed Construction	Defendant's Proposed Construction
"labeled terminators"	"a terminator which is modified with a moiety which permits discovering the presence or existence of a specific nucleic	"a terminator attached to which is a moiety, the identity of which is determined using the moiety's distinguishable properties"

Term	Plaintiffs' Proposed Construction	Defendant's Proposed Construction
	acid or nucleic acid sequence using autoradiography or scintillation counting, fluorescence or absorption spectroscopy, mass spectrometry, enzyme activity, or other methods" "terminator" means "a nucleotide or nucleotide analog which, after being incorporated onto the 3' end of a primer, does not permit any further extension of the primer"	

91. One of ordinary skill in the art would understand the claim term "labeled terminator" means "a terminator which is modified with a moiety which permits discovering the presence or existence of a specific nucleic acid or nucleic acid sequence using autoradiography or scintillation counting, fluorescence or absorption spectroscopy, mass spectrometry, enzyme activity, or other methods."

92. In the context of the claims in the patents-in-suit, one of ordinary skill in the art would understand that when a terminator is "labeled," it means the terminator has been modified with a "detectable marker," i.e., with a moiety which permits discovery of the presence or existence of a specific nucleic acid or nucleic acid sequence using autoradiography or scintillation counting, fluorescence or absorption spectroscopy, mass spectrometry, enzyme activity using a protein moiety, or other methods. See discussion in Section VII.C for terminator, Section VII.B for detectable label, and Section VII.D for "labeled with a detectable marker."

93. I disagree with Defendant's proposed construction of "labeled terminator," which I understand is "a terminator attached to which is a moiety, the identity of which is determined using the moiety's distinguishable properties." Defendant's proposed construction of this term is incorrect for the reasons set forth above relating to the terms "terminator" and "labeled with a detectable marker."

F. "wherein at least one of said terminators is labeled with a detectable marker" in the '819 patent (claims 1, 43, 46 and 47)

Term	Plaintiffs' Proposed Construction	Defendant's Proposed Construction
"wherein at least one of said terminators is labeled with a detectable marker"	"wherein at least one of the terminators is modified with a moiety which permits discovering the presence or existence of a specific nucleic acid or nucleic acid sequence using autoradiography or scintillation counting, fluorescence or absorption spectroscopy, mass spectrometry, enzyme activity, or other methods" "terminator" means "a nucleotide or nucleotide analog which, after being incorporated onto the 3' end of a primer, does not permit any further extension of the primer"	"wherein at least one of said terminators has attached a moiety, the identity of which is determined using the moiety's distinguishable properties"

94. One of ordinary skill in the art would understand the claim language "wherein at least one of said terminators is labeled with a detectable marker" means "wherein at least one of said terminators is modified with a moiety which permits discovering the presence or existence of a specific nucleic acid or nucleic acid sequence using autoradiography or scintillation counting, fluorescence or absorption spectroscopy, mass spectrometry, enzyme activity, or other methods."

95. The terms "terminators," "labeled," and "labeled with a detectable marker" have the meanings as described above.

96. I disagree with Defendant's proposed construction of "wherein at least one of said terminators is labeled with a detectable marker," which I understand is "wherein at least one of said terminators has attached moiety, the identity of which is determined using the moiety's distinguishable properties." This proposed construction is incorrect for the reasons described above relating to Defendant's proposed constructions of "terminator" and "labeled with a detectable marker."

G. "by detecting the detectable marker of said incorporated terminator" in the '819 patent (claims 1, 43, and 47)

Term	Plaintiffs' Proposed Construction	Defendant's Proposed Construction
"by detecting the detectable marker of said incorporated terminator"	"by discovering the presence or existence of a moiety of the incorporated terminator using autoradiography or scintillation counting, fluorescence or absorption spectroscopy, mass spectrometry, enzyme activity, or other methods" "terminator" means "a nucleotide or nucleotide analog which, after being incorporated onto the 3' end of a primer, does not permit any further extension of the primer"	"by determining the identity of the detectable marker attached to said incorporated terminator using the detectable marker's distinguishable properties"

97. One of ordinary skill in the art would understand the claim term "by detecting the detectable marker of said incorporated terminator" means "by discovering the presence or existence of a moiety of the incorporated terminator using autoradiography or scintillation counting, fluorescence or absorption spectroscopy, mass spectrometry, enzyme activity, or other methods." This construction is appropriate for the reasons set forth above concerning the term "detectable marker."

98. I disagree with Defendant's proposed construction is "by detecting the detectable marker of said incorporated terminator," which I understand is "by determining the identity of the detectable marker attached to said incorporated terminator using the detectable marker's distinguishable properties." This construction is incorrect for the reasons set forth above concerning the terms "detectable marker" and "terminator."

H. "at least one of the terminators being labeled with a detectable marker" '744 patent (claim 1) and the '748 patent (claim 1)

Term	Plaintiffs' Proposed Construction	Defendant's Proposed Construction
"at least one of the terminators being labeled with a detectable marker""	"at least one of the terminators being labeled with a detectable marker" means "a terminator which is modified with a moiety which permits discovering the presence or existence of a specific nucleic acid or nucleic acid sequence using autoradiography or scintillation counting, fluorescence or absorption spectroscopy, mass spectrometry, enzyme activity, or other methods" "terminator" means "a nucleotide or nucleotide analog which, after being incorporated onto the 3' end of a primer, does not permit any further extension of the primer"	"at least one of the terminators has attached a moiety, the identity of which is determined using the moiety's distinguishable properties"

99. One of ordinary skill in the art would understand the claim term "at least one of the terminators being labeled with a detectable marker" means "a terminator which is modified with a moiety which permits discovering the presence or existence of a specific nucleic acid or nucleic acid sequence using autoradiography or scintillation counting, fluorescence or absorption spectroscopy, mass spectrometry, enzyme activity, or other methods."

100. The terms "terminators," "labeled," and "labeled with a detectable marker" have the same meaning as described above.

101. I disagree with Defendant's proposed construction of "at least one of the terminators being labeled with a detectable marker," which I understand is "at least one of said terminators has attached a moiety, the identity of which is determined using the moiety's distinguishable properties." This proposed construction is incorrect for the reasons described above relating to Defendant's proposed constructions of "terminator," "detectable marker" and "labeled with a detectable marker."

VIII. SUPPLEMENTATION

102. I may supplement this declaration if I become aware of additional pertinent information or in response to the testimony of others, including any expert testimony offered by Defendant. Moreover, I may comment on, or testify in response to, the testimony of other witnesses, including witnesses who testify or submit reports or declarations on behalf of Defendant.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct to the best of my knowledge and belief.

Executed this 3rd day of April, 2009, in Philadelphia, Pennsylvania.

Larry J. Kricka

LARRY J. KRICKA

UNIVERSITY OF PENNSYLVANIA - SCHOOL OF MEDICINE
Curriculum Vitae

Date: January 2009

LARRY J. KRICKA, D.Phil., F.A.C.B., C. Sci., C.Chem., F.R.S.C., F.R.C.Path.

Home Address: 654 Dorset Road, Devon, PA 19333

Office Address: Department of Pathology and Laboratory Medicine
University of Pennsylvania Medical Center
3400 Spruce Street
Philadelphia, PA 19104

Education:

1965-68	B.A. (Hons) York University, York, UK (Chemistry)
1968-71	D.Phil. York University, York, UK (Chemistry)

Postgraduate Training and Fellowship Appointments:

1971-73	Research Assistant, Liverpool University, Liverpool, UK
1981-82	Medical Research Council Traveling Fellow, University of California at San Diego, San Diego, CA

Military Service: None

Faculty Appointments:

1973-80	Lecturer, Clinical Chemistry, Birmingham University, Birmingham, UK
1980-87	Senior Lecturer, Clinical Chemistry, Birmingham University, Birmingham, UK
1987-87	Reader in Clinical Chemistry, Birmingham University, Birmingham, UK
1987-	Professor, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA
1987-	Director, General Chemistry Laboratory, Hospital of the University of Pennsylvania, Philadelphia, PA.
2000-01	Acting Director of Clinical Chemistry Section, Hospital of the University of Pennsylvania, Philadelphia, PA.
2002-02	Distinguished Visiting Scholar, Christ's College, Cambridge, England

Hospital and Administrative Appointments:

1981-87	Honorary Consulting Officer in Clinical Chemistry, Central Birmingham Health District, Birmingham, UK
1982-87	Head of Development Laboratory, Wolfson Research, Birmingham, UK Laboratories, Queen Elizabeth Medical Centre, Birmingham, UK

Specialty certification: Royal College of Pathologists (UK)

Awards, Honors and Membership in Honorary Societies:

1966	Whinfield Essay Prize (York University, York, UK)
1970	Kathleen Mary Stott Research Prize (York University, York, UK)

1981	SAC Silver Medal (Royal Society of Chemistry, London, UK)
1983	Fellow of the Royal Society of Chemistry (London, UK)
1983	Membership of the Royal College of Pathologists (London, UK)
1985	British Technology Group Academic Enterprise Competition (Joint 2nd)
1986	Department of Trade and Industry, Industry Year Award for Technology Transfer (commendation)(DTI, London, UK)
1989	Prince of Wales Award for Innovation and Production (citation)
1990	Queens Award for Technological Achievement (jointly with colleagues from the Wolfson Research Laboratories and Amersham International
1991	Rank Prize for Opto-Electronics (Jointly with colleagues from the Wolfson Research Laboratories)(Rank Prize Funds, London, UK)
1991	Fellow, Royal College of Pathologists
1993	Voted one of "66 Philadelphians Changing the Face of America", Philadelphia Magazine (November 1993)
1995	Certificate of Honor, American Association for Clinical Chemistry, New Jersey Section
1997	Kubasik Lecture Award, Upstate New York Section, American Association for Clinical Chemistry
1998	AACC Award. Outstanding Contributions to Clinical Chemistry in a Selected Area of Research
2000	Fellow, National Academy of Clinical Biochemistry
2000	Reimer Award, American Association for Clinical Chemistry, Capital Section
2002	Outstanding Speaker Award, American Association for Clinical Chemistry
2005	Outstanding Speaker Award, American Association for Clinical Chemistry
2006	Fellow, International Union of Pure and Applied Chemistry
2006	Ullman Award, Award, American Association for Clinical Chemistry
2007	Royal Society of Chemistry, Chartered Scientist

Memberships in Professional and Scientific Societies:
Royal Society of Chemistry (Fellow)
Royal College of Pathologists (Member 1983-1991, Fellow 1991)
Association of Clinical Biochemists (Honorary member 2004)
American Association for Clinical Chemistry
National Academy of Clinical Biochemistry (Fellow)

Editorial Positions:

1980-97	Editorial Board, Talanta
1983 -	Editorial Board, Analytical Biochemistry
1984-87	Joint Editor, Biotechnology News (Birmingham University)
1985-	Editor-in-Chief, Journal of Bioluminescence and Chemiluminescence
1988-95	Editorial Board, Journal of Immunoassay
1998-2000	Editorial Board, Clinical Chemistry Journal (AACC)
2002-	Editorial Board, Clinical Chemistry Journal (AACC)
2002-	Editorial Board, Lab-on-a-Chip (RSC)
2002	Editorial Advisory Board Member, Encyclopedia of Diagnostic Genomics and Proteomics (Fuchs, J., and Podda, M., eds.) Marcel Dekker Inc.
2003	Editorial Board, Journal of Medical Sciences
2004-5	Editorials Editor, Clinical Chemistry Journal (AACC)
2006-	Associate Editor, Clinical Chemistry Journal (AACC)

2006- Editorial Board, SciAlert
2008- Editorial Board, Biomarkers in Medicine

Ad Hoc Reviewer: Analyst, Analytical Biochemistry, Analytical Chemistry, Analytical Letters, Annals of Clinical Biochemistry, Biosensors Biolelectronics, BioTechniques, Canadian Journal of Chemistry, Clinical Biochemistry, Clinical Chemistry, Experimental Cell Research, Journal of Bioluminescence and Chemiluminescence, Journal of Immunoassay, Journal of Immunological Methods, Lab-on-a chip, Laboratory Investigation, Nucleic Acids Research, Proceedings of the Mayo Clinic.

Academic Committees at the University of Pennsylvania: Reinhold Lecture Committee, Informatics Committee, SICU Executive Committee, AutoLab Committee, Resident Advisory Committee (RAC, REACH), School of Medicine Faculty IP Committee

Major Teaching and Clinical Responsibilities at the University of Pennsylvania : Pathology 100, Pathology 301, Pathology 305, Curriculum 2000, Bioengineering course, Resident training course, MTR 603 Disease Measurements, Frontiers in Medical Science 505

Ad Hoc Reviewer: National Institutes of Health, National Science Foundation, Ben Franklin Fund, Medical Research Council (UK), Medical Research Council (Canada), University of Turku (Finland), Italian Ministry for Education, University and Research (Italy).

Postgraduate activities: Advisor for Ph.D. and M.Sc. theses (University of Birmingham, UK), and M.Sc. advisor (Drexel University, Philadelphia, PA). External examiner for Ph.D. theses (University of Belfast, Belfast, Northern Ireland and University of Sussex, Brighton, UK). Undergraduate thesis advisor (University of Bologna, Italy).

Commonwealth of Pennsylvania Committees:
1994 New Technology Health Planning Task Force

International Advisory and Educational Activities:
Consultant, World Health Organization
1981 Milan, Italy, Immunoassay Course
1982 Mexico City, Mexico, Immunoassay Course
1984 Geneva, Switzerland, Immunoassay Committee

Consultant, British Council
1985 Harare, Zimbabwe, Chemical Pathology Course

Visiting Professor
1995 University of Bologna, Bologna, Italy
1999 Tsinghua University, Beijing, China

National Heart, Lung and Blood Institute
2003 Working Group on Proteomics

National and International Offices:
1984-96 Secretary, International Organizing Committee, International Symposium on Bioluminescence and Chemiluminescence

1989 -	Scientific Committee, International Symposium on Quantitative Luminescence Spectrometry in Biomedical Sciences
1989-90	Co-organizer, VI International Symposium on Bioluminescence and Chemiluminescence, Cambridge, England.
1988-89	Chair Elect, Philadelphia Section, American Association for Clinical Chemistry
1989-90	Chair Philadelphia Section, American Association for Clinical Chemistry
1991-92	Chair, Membership Committee, American Association for Clinical Chemistry
1990-94	Member, Endo LIP Committee, American Association for Clinical Chemistry
1990-91	Chair, Symposium Committee, Clinichem '91 Organizing Committee
1991	Chair, Special Topics Session, Oak Ridge Conference, American Association for Clinical Chemistry, St. Louis, MO
1991-94	Conference Committee, Oak Ridge Conference, American Association for Clinical Chemistry
1991-93	Chair, Symposium Committee, American Association for Clinical Chemistry National Meeting, New York, NY
1992-96	Member, Book Committee, American Association for Clinical Chemistry
1992-93	Chair, Symposium Committee, Clinichem '93
1993-94	Chair, Special Topics Session, Oak Ridge Conference, American Association for Clinical Chemistry, Tampa, FL
1993-94	Chair, Symposium Committee, Clinichem '94
1993-98	Member, Immunology Division Committee, American Association for Clinical Chemistry
1994-96	Chair, Oak Ridge Conference Committee, American Association for Clinical Chemistry
1996-7	Chair, Clinichem'97
1997-98	Member, CAT Committee, IFCC
1997-99	Member, Board of Directors, American Association for Clinical Chemistry
1998-99	Chair, IFCC CAT Committee, IFCC
1998-00	Board of Editors, Clinical Chemistry Journal
1999-	Chair, IFCC Working Group on Microtechnology, IFCC
2000	President-Elect, American Association for Clinical Chemistry
2001	President, American Association for Clinical Chemistry
2002	Past-President, American Association for Clinical Chemistry
2002-3	Member, House of Delegates Steering Committee, American Association for Clinical Chemistry
2002-	Publications Officer, International Society for Bioluminescence and Chemiluminescence
2002-6	NCCLS committee on Diagnostic nucleic acid arrays (MM-12P)
2003-4	Chair, Oak Ridge Committee, American Association for Clinical Chemistry
2003	Working Group on Proteomics, NHLBI
2004-5	Member, Oak Ridge Committee, American Association for Clinical Chemistry
2005-	Program Coordinating Committee, American Association for Clinical Chemistry
2006-8	Vice Chair, 2008 AACC Annual Meeting organizing Committee
2006-8	Member, San Diego Conference Committee, American Association for Clinical Chemistry
2007-8	Member, CDC Institute: Managing for Better Health
2008	President Elect, International Society for Bioluminescence and Chemiluminescence

Selected Lectures by Invitation: (recent only)

3/2007	"Technology solutions for the analytical demands of pathology and laboratory medicine", Royal College of Pathologists of Australia, Pathology Update 2007, Sydney, Australia.
4/2008	"Interferences in immunoassays", ASCLS-PA Spring Meeting, King of Prussia, PA.
9/2008	"Point-of-care technologies for the future. Technological innovations and hurdles to implementation", AACC POC Symposium, Barcelona, Spain.
9/2008	"Quality control and quality assurance of microarray-based assays", 20th International Congress of Clinical Chemistry and Laboratory Medicine, Fortaleza, Brazil.
10/2008	"Automation of clinical laboratory testing", Shanghai Medical Association Meeting, Shanghai, China.

News and magazine articles: Articles covering my research work have appeared in The Wall Street Journal (April, 1993), and the Philadelphia Inquirer (April, 1993). Featured in Philadelphia Magazine (November, 1993) Cutting Edge Philadelphians article. Radio interviews for stations in Sweden and Australia and TV interview for a station in Cairo, Egypt.

Who's Who in America: Entered into the 2002 edition (Who's Who in America, Marquis; Providence, NJ. 56th edn., 2002, p 2946)

Bibliography:

Research Publications, peer reviewed

1. Kricka L.J., Vernon J.M.: Reactions involving deamination of isoindole adducts with acetylenic dienophiles. Chemical Communications, 942-943, 1971.
2. Kricka L.J., Vernon J.M.: Autoxidation of poly-substituted isoindoles. Journal of the Chemical Society, Part C, 2667-2670, 1971.
3. Kricka L.J., Vernon J.M.: Reactions of some isoindoles with acetylenic esters. Journal of the Chemical Society, Perkin 1, 904-908, 1972.
4. Kricka L.J., Ledwith A.: Reactions of condensed N-heteroaromatic molecules. Part 1. Alkylation by thallium (I) ethoxide. Journal of the Chemical Society, Perkin 1, 2292-2293, 1972.
5. Kricka L.J, Ledwith A.: Cation Radicals: Reactions of methoxylated benzil and bibenzyl derivatives with tris-(p-bromophenyl) ammoniumyl hexachloroantimonate. Journal of the Chemical Society, Perkin 1, 294-297, 1973.
6. Hyde P, Kricka L.J., Ledwith A.: Synthesis and polymerisability of N-ethyl-2-vinylcarbazole. Polymer, 14, 124-125, 1973.
7. Kricka L.J., Vernon J.M.: Deamination of napthalen-1,4-imines and anthracen-9,10-imines by reactions with benzyne or dimethyl acetylene dicarboxylate. Journal of the Chemical Society, Perkin 1, 766-771, 1973.
8. Kricka L.J., Ledwith A.: Reactions of condensed N-heteroaromatic molecules. Part II. Electrophilic substitution of N-acetylcarbazole, N-acetyl-10,11-dihydrobenzazepine and derivatives. Journal of the Chemical Society, Perkin 1, 859-863. 1973.
9. Abraham R.J, Kricka L.J., Ledwith A.: Concerted rotational- inversion process in 5-acyl-10,11-dihyrobenz-[b,f]azepines. Chemical Communications, 282-283, 1973.
10. Kricka L.J, Lambert M.C., Ledwith A.: Photochemical cyclodimerisation and rearrangement of 5H-dibenz-[b,f]azepines derivatives. Chemical Communications, 244-245, 1973.
11. Hyde P, Kricka L.J., Ledwith A.: N-Acryloyldibenz[b,f]azepine - A new monomer for the synthesis of photo-crosslinkable co-polymers. Polymer Letters, 11, 415-419, 1973.
12. Kricka L.J,. Ledwith A.: Reactions of vinyl acetate with carbazole. Journal of Organic Chemistry, 38, 2240-2241, 1973.
13. Kricka L.J., Lambert M.C., Ledwith A.: Reactions of condensed N-heteroaromatic molecules. Part III. Photo-chemical reactivity and acylation of N-acyldibenz [b,f]azepines and derivatives. Journal of the Chemical Society, Perkin 1, 52-57, 1974.
14. Hyde P, Kricka L.J., Smith K.C.: Synthesis and polymerizability of 5-N-methyl-2-vinyliminobibenzyl and 10-ethyl-2-vinylphenothiazine. Polymer, 15, 387-389, 1974.
15. Kricka L.J., Vernon J.M.: Some derivatives of 2,5-xylidine and their cyclisation to indoles. Canadian Journal of Chemistry, 52, 299-302, 1974.
16. Beresford P., Iles D.H., Kricka LJ, Ledwith A.: Cation radicals: oxidative coupling of carbazoles, 10,11-dihydro-5H-dibenz[b,f]azepines and related derivatives by 2,3-dichloro-5,6-dicyano-*p*-benzoquinone and tris-(p-bromo-phenyl) ammoniumyl salts. Journal of the Chemical Society, Perkin I, 276-280, 1974.

17. Abraham, R. J., Kricka, L. J., Ledwith A.: The nuclear magnetic resonance spectra and conformation of cyclic compounds. Part X. Conformational equilibria in 5-substituted-10, 11-dihydrodibenz[b,f]azepines. Journal of the Chemical Society, Perkin II, 1648-1654, 1974.

18. Bell, F.A., Beresford, P., Kricka, L.J., Ledwith A.: Cation radicals: reactions of cation radicals from substrates containing a *p*-dimethylaminophenyl group. Journal of the Chemical Society, Perkin I, 1788-1792, 1974.

19. Ahmed M., Kricka L.J., Vernon J.M.: Autoxidation of polysubstituted isoindoles. Part II. Products from 1,3-diphenyl- and 1,2,3-triphenyl-isoindoles. Journal of the Chemical Society, Perkin I, 71-75, 1975.

20. Kennedy J.H., Kricka L.J., Whitehead T.P., Wilding P.: Evaluation of protein-protein coupling reagents. In: Organisation Des Laboratoires - Biologie Prospective, III^{e} Colloque de Pont-a-Mousson, L'Expansion Scientifique Francaise, Paris, pp. 631-634, 1975.

21. Kennedy J.H., Kricka L.J., Wilding P.: The application of thin-layer gel filtration chromatography in the rapid assessment of protein-protein coupling reactions. Journal of Chromatography, 118, 337-343, 1976.

22. Kennedy J.H., Kricka L.J.: Low cost apparatus for thin layer gel filtration chromatography. Laboratory Practice, 25, 471-472, 1976.

23. Kennedy J.H., Kricka L.J., Wilding P.: A comparison of one-stage, multi-stage and protected reactions for the coupling of peroxidase to proteins. Protides of the Biological Fluids, 24, 787-794, 1976.

24. Kricka L.J., Carter T.J.N.: A method for enhancing the stability of thiol-containing enzymes immobilised on nylon. Clinica Chimica Acta, 79, 141-147, 1977.

25. Clark P.M.S., Kricka L.J.: Interferences by diazepam in the determination of 5-hydroxyindole-3-acetic acid. Annals of Clinical Biochemistry, 14, 233-234, 1977.

26. Vernon J.M., Ahmed M., Kricka L.J.: Reactions of 5,6,7,8-tetrahalogeno-1,4-dihydronaphthalen-1,4-imines with dimethyl acetylenedicarboxylate. Journal of the Chemical Society, Perkin I, 837-842, 1978.

27. Akhter M.I., Clark P.M.S., Kricka L.J., Nicholson G.: Urinary metabolites of tryptophan, serotonin and norepinephrine in alcoholics. Journal of Studies on Alcohol, 78, 833-841, 1978.

28. Clark P.M.S., Kricka L.J.: The quality of materials employed as standards in urea, uric acid and bilirubin determinations. In: Biologie Prospective IV^{e} Colloque de Pont-a-Mousson, Masson, Paris, pp. 467-471, 1978.

29. Carter T.J.N., Kricka L.J., Whitehead T.P.: The bioluminescent determination of substrates using NAD dependent oxido-reductase enzymes. Protides of the Biological Fluids, 26, 643-646, 1978.

30. Carter T.J.N., Kricka L.J., Stanbridge B.R.: Immobilised enzymes as laboratory reagents: Modification of the pH optimum of immobilised glucose oxidase. Protides of the Biological Fluids, 26, 661-664, 1978.

31. Wilding P., Bullock D.G., Kricka L.J., Morris R., Holder R.L.: Spectral analysis of urinary reactions: A preliminary study based on a novel concept. Clinical Chemistry, 25, 476-480, 1979.
32. Burt S.M., Carter T.J.N., Kricka L.J.: Thermal characteristics of microtitre plates used in immunological assays. Journal of Immunological Methods, 31, 231-236, 1979.
33. Ham G., Belcher R., Kricka L.J., Carter T.J.N.: Stability of trace iodine solutions. Analytical Letters, 12, 535-541, 1979.
34. Clark P.M.S., Kricka L.J., Patel A.: Purity and stability of urea, creatinine and uric acid standards. Analytical Letters, 12, 1537-1549, 1979.
35. Macartney J.C., Trevethick M.A., Kricka L.J., Curran R.C.: Identification of myosin in human epithelial cancers with immunofluorescence. Laboratory Investigation, 41, 437-445, 1979.
36. Thorpe G.H.G., Kricka L.J., Carter T.J.N., Whitehead T.P.: A comparison of various separation procedures for bacterial luciferase/reductase. In: Proceedings: International Symposium on Analytical Applications of Bioluminescence and Chemiluminescence, State Publishing and Printing, Westlake Village, CA, pp. 154-165, 1979.
37. Carter T.J.N., Kricka L.J., Bullock D.G., Bunce R.A., Whitehead T.P.: The optimisation of luminescence instrumentation. In: Proceedings: International Symposium on Analytical Applications of Bioluminescence and Chemiluminescence, State Publishing and Printing, Westlake Village, CA, pp. 637-651, 1979.
38. Carter T.J.N., Kricka L.J., Morriss P., Holder R., Whitehead T.P.: Computer modelling as an aid to the use of NADH - linked bacterial luminescence system in clinical analysis. In: Proceedings: International Symposium on Analytical Applications of Bioluminescence and Chemiluminescence, State Publishing and Printing, Westlake Village, CA, pp. 652-662, 1979.

39. Clark P.M.S., Kricka L.J., Whitehead T.P.: Pattern of urinary proteins and peptides in patients with rheumatoid arthritis investigated with the Iso-Dalt technique. Clinical Chemistry, 26, 201-204, 1980.
40. Kricka L.J., Carter T.J.N., Burt S.M., Kennedy J.H., Halliday M.I., Teleford M.E., Wisdom G.B.: Variabilityy in the properties of microtitre plates used as solid supports in enzyme-immunoassay. Clinical Chemistry, 26, 741-744, 1980.
41. Clark P.M.S., Kricka L.J., Patel A.: High performance liquid chromatographic assessment of the quality of materials employed as calibration standards in creatinine, urea, uric acid and bilirubin determinations. Journal of Liquid Chromatography, 3, 1031-1046, 1980.
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CERTIFICATE OF SERVICE

I hereby certify that counsel of record who are deemed to have consented to electronic service are being served on April 3, 2009, with a copy of this document via the Court's CM/ECF system per Local Rules and Administrative Policies Section 2(d).

Any other counsel of record will be served by electronic mail, facsimile transmission and/or first class mail on this same date.

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